

June 2013

NIEHS Spotlight



[Council approves concepts, shares budget concerns](#)

Members were updated on recent activities and achievements, grappled with implications of ongoing budget restrictions, and voted to approve three concepts for new initiatives.



[NIEHS career fair showcases career options](#)

The 16th annual NIEHS Biomedical Career Fair took place April 26 on the U.S. Environmental Protection Agency's campus in Research Triangle Park, N.C.



[Ethics Day draws capacity crowd](#)

Creative planning helped organizers make the 4th annual Ethics Day May 21 another fun and interesting experience for people from all sectors of NIEHS.



[Researchers bring environmental health perspective to pediatrics meeting](#)

Director Linda Birnbaum, Ph.D., and NIEHS grantees were plenary presenters at the high-profile Pediatric Academic Societies meeting May 4-7 in Washington, D.C.



[ONES awardee elected to American Society for Clinical Investigation](#)

NIEHS grantee Gokhan Mutlu, M.D., was one of 80 early-career physician scientists inducted into the American Society for Clinical Investigation for 2013.

Science Notebook



[Katsuhiko Mikoshiba delivers 2013 Rodbell Lecture](#)

The prestigious Dr. Martin Rodbell Lecture April 30 went international this year with Katsuhiko Mikoshiba, M.D., Ph.D., as its fifteenth speaker.



[Davidian explores the role of statistics in personalized medicine](#)

During her distinguished lecture May 8, Marie Davidian, Ph.D., focused on the role statistical methods will need to play in developing personalized treatment strategies.



[Science talks on EDCs and smoking update Council](#)

Members heard presentations on the state of the science for endocrine disrupting chemicals and findings on genome-wide interactions with smoking.



[ONES program celebrates seventh year of excellence](#)

At the annual meeting May 20-21, there was even more than usual to cheer, as the program looked forward to its renewal after a yearlong hiatus.



[Barium distributions in teeth reveal early-life dietary transitions](#) ▶ Audio

A new NIEHS-funded study in the journal Nature shows that chemical signatures in teeth can be used to uncover aspects of early life dietary transitions.

NIEHS Spotlight



[Former NIEHS STEP student encourages others to dream big](#)

Brian Rogers' career path took a wonderfully circuitous route, and he wants to inspire others to believe in themselves, too.



[NTP researchers win International Society for Neurochemistry recognition](#)

Scientists in the NTP Laboratory Neurotoxicology Group earned recognition this year in the International Society for Neurochemistry Advanced School.



[Superfund graduate trainees win foundation support](#)

The careers of University of Arizona graduate students Linnea Herbertson and Corin Hammond gained momentum this spring with foundation awards.



[Grantees honored for breast cancer risk communication](#)

Three members of the Michigan State University Breast Cancer and the Environment Research Program are winners of the 2013 Applied Research Award.



[NIEHS fellow launches a career in science administration](#)

Ashley Godfrey, Ph.D., completed her four-year postdoctoral training at NIEHS and in May joined the Duke Cancer Institute as a scientific review officer.



[Trainee meeting focuses on workforce trends](#)

As the annual general meeting of the NIEHS Trainees Assembly May 10 underscored, career development is more important than ever in today's market.

Science Notebook



[NIEHS scientists identify a novel signal for mismatch repair](#)

In a new study published in *Molecular Cell*, researchers report uncovering an identification signal on the newly copied DNA strand that marks it for repair.



[New plant research discoveries could benefit global agriculture](#)

Research supported in part by NIEHS is addressing big questions about plant growth and offers potential solutions for meeting increased agricultural demand.



[Researchers at NIEHS discover role for a unique complex in DNA repair](#)

Chromosome Stability Group research characterizes key proteins involved in homology-driven recombinational repair, a mechanism of DNA double-strand break repair.



[Superfund program director discusses mining waste solutions in Armenia](#)

Raina Maier, Ph.D., director of the University of Arizona SRP Center and an expert in environmental microbiology, spoke on phytostabilization of mining waste.



[Congressional briefing highlights organs-on-a-chip](#)

The May 15 briefing on biomimetic microsystems on Capitol Hill was sponsored by the Congressional Biomedical Research Caucus.

NIEHS Spotlight



[UW centers co-host Duwamish River Superfund cleanup forum](#)

The meeting was part of the Duwamish River Cleanup Coalition's outreach plan to educate the university community about an EPA cleanup proposal.



[Postdocs showcase outreach program at local school](#)

Members of the NIEHS community turned out May 2 to show their support for outreach efforts by Institute trainees at Lowe's Grove Middle School in Durham, N.C.

Inside the Institute



[NIEHS employees flex muscles during Health and Fitness Week](#)

This year's Seattle-like cool, damp spring weather April 29-May 3 failed to detour enthusiasts from indoor events or from the high-profile outdoor competitions.



[Mueller talks weird science at RTP event](#)

NIEHS Associate Staff Scientist Geoffrey Mueller, Ph.D., was one of ten local scientists featured April 16 at the 180 Degree series event Weird Science.

Science Notebook



[Smartphone technology makes exposure assessment more personal](#)

The CalFit smartphone application improves air pollution exposure assessment by providing personal data on time-location patterns and physical activity.



[Early life socioeconomic factors influence development of rheumatoid arthritis](#)

Growing evidence, including a new study on rheumatoid arthritis by scientists at NIEHS, shows that exposures in early life can have long-term impacts on health.



[Superfund researchers well represented at combustion research meeting](#)

Leaders from academia, government, and industry gathered in New Orleans May 15-18 for the 13th International Congress on Combustion By-Products and Their Health Effects.



[Researchers pinpoint gene expression changes associated with human cancers](#)

The new study showed that gene expression changes associated with tumor-related metabolism vary significantly across 22 types of human tumors.



[This month in EHP](#)

This month's Environmental Health Perspectives highlights environmental justice issues related to hog farming and the matrix of risk for elevated blood lead in refugee children.

Calendar of Upcoming Events

- **June 4**, in the Executive Conference Room, 12:00-1:00 p.m. — Receptor Mechanisms Discussion Group presentation by David Collier, M.D., Ph.D., discussing “Xenobiotic Obesogens and Childhood Obesity: A Clinical Perspective”
- **June 6 (offsite event)**, at North Carolina State University College of Veterinary Medicine, Room D-239, 12:15-1:15 p.m. — Molecular Biomedical Sciences Seminar featuring a presentation by Joseph Graziano, Ph.D., on “Poison in the Well: Exposure, Consequences, and Remediation of Arsenic in Bangladesh” ([directions and parking](#))
- **June 10-12 (offsite event)**, at the World Health Organization headquarters in Geneva — International Meeting on Electronic Waste and Children
- **June 11-12 (offsite event)**, at the Omni Shoreham Hotel in Washington, D.C. — Joint workshop on safety culture with the NIEHS Worker Education and Training Program, National Institute for Occupational Safety and Health, and Center for Construction Research and Training
- **June 15-18 (offsite event)**, at the Moscone Center in San Francisco — Endocrine Society [annual meeting](#)
- **June 25**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — NTP Board of Scientific Counselors
- **June 26**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — Workshop on identifying opportunities for global integration of toxicogenomics databases
- **June 30-July 4 (offsite event)**, in Seoul, South Korea — 14th International Congress of Toxicology
- View More Events: [NIEHS Public Calendar](#)

Extramural Research

[Extramural papers of the month](#)

- [Elevated numbers of copy number variants linked with autism](#)
- [How dietary omega-3s reduce tumor growth](#)
- [Air pollution associated with increased risk for serious birth defects](#)
- [Text mining improves chemical-gene-disease curation](#)

Intramural Research

[Intramural papers of the month](#)

- [DNA methylation could predict breast cancer risk](#)
- [The mechanism of action of a natural estrogenic compound](#)
- [Human mitochondrial DNA polymerase ineffectively repairs acrolein-induced adducts](#)
- [Coordinating DNA double strand break repair at both ends](#)

NIEHS Spotlight

Council approves concepts, shares budget concerns

By Ernie Hood

During the spring National Advisory Environmental Health Sciences Council meeting May 14-15, members were updated on a variety of recent NIEHS activities and achievements, grappled with implications of ongoing budget restrictions, and voted to approve three concepts for new initiatives (see [text box](#)).

NIEHS and NTP Director Linda Birnbaum, Ph.D., and Division of Extramural Research and Training (DERT) Director Gwen Collman, Ph.D., presented the latest Institute developments in their reports. Council also enjoyed two scientific presentations (see [story](#)), and heard talks on NIH initiatives related to the Big Data initiative and proposed new approaches in the NIEHS Environmental Health Sciences (EHS) Core Centers program.

Budget cuts and continued uncertainty

Budget issues are often a high priority at Council, and this meeting was no exception, given the current situation. The federal government is operating under a continuing resolution until the end of the fiscal year Sept. 30, and the across-the-board sequestration cuts went into effect March 1. Birnbaum said that intramural programs have been cut by 4.6-4.7 percent and the grants program has been reduced more than 5.5 percent, with about 20 fewer grants being funded this year than had been anticipated. However, she noted, “Because we have had a soft hiring freeze for the past two years, we have not had to furlough any of our federal staff.”

On a brighter note, as part of her overall update to Council on recent NIEHS achievements and activities, Birnbaum reported that implementation of the new NIEHS strategic plan is progressing well. Leadership is currently reviewing reports from the eight teams addressing the cross-divisional, overlapping areas of the plan. “We are currently getting close to finalizing the leadership directions for how these activities will go forward,” she said.



Birnbaum maintained a sunny disposition, in light of unrelenting budget pressures, enjoying several light-hearted moments with Council. (Photo courtesy of Steve McCaw)



Council members, from left, Marie-Francoise Chesselet, M.D., Ph.D., of UCLA; Tom Gasiiewicz, Ph.D., of the University of Rochester; and Mary Lee, M.D., of the University of Massachusetts, joined in a humorous moment of their own, during Council proceedings. (Photo courtesy of Steve McCaw)

Extramural activities

Implementation of the new strategic plan is driving much of the activity in DERT these days, as the division strives to align its programs with the major elements of the plan. Part of that effort is to comprehensively assess baseline investments across the grants portfolio, to provide a benchmark for systematic, ongoing analysis of how the portfolio changes and grows in different ways, along with the strategic plan concepts.

Collman also described a proposed reorganization of the division. While the Worker Education and Training, and Program Analysis branches would remain as they are, the other programmatic areas would be redefined to align with the goals of the strategic plan. The new branches would be the Genes, Environment, and Health Branch; Exposure, Response, and Technology Branch; Population Health Branch; and Hazardous Substances Research Branch.

There will be a public webinar about the reorganizations June 6, from 1:00 to 2:00 p.m. EST, for public input and comment. Collman will discuss the implementation of the NIEHS Strategic Plan in DERT and the Division's investment across the 11 goals. She will present a proposed organizational strategy to fully implement the Strategic Plan within the Division and said looks forward to feedback from interested parties, as well as the general public.

Those interested in participating should RSVP before June 6 by emailing derpublicmeeting@niehs.nih.gov to receive the link to the webinar. Information on any special accommodations needed should be included in the message.

Tackling Big Data

NIEHS Senior Advisor Allen Dearry, Ph.D., described two new NIH initiatives designed to alleviate the biomedical big data bottleneck — Big Data to Knowledge and InfrastructurePlus. Both programs are to be led by trans-NIH advisory data councils, with shared investment, from the NIH Common Fund and individual institutes and centers, totaling approximately \$100 million over 5-7 years.

“In some ways, we’ve been the victim of our own success,” Dearry told Council. “And in many ways, this issue of how to deal with the data, where to store the data, how to handle the data, how to analyze the data, how to produce results from the data, has become the major bottleneck in biomedical research.”



“DERT has really embraced the strategic plan with a lot of enthusiasm and new ideas and energy,” Collman told Council. “The next step is to rework the configuration of the division, in a way that allows us to do more in-depth, creative work around the strategic plan goals.” (Photo courtesy of Steve McCaw)



It was the first Council meeting for new members Norbert Kaminski, Ph.D., of Michigan State University, left, and Linda McCauley, Ph.D., R.N., of Emory University. (Photo courtesy of Steve McCaw)

EHS Centers

Health Scientist Administrator Les Reinlib, Ph.D., described proposed new guidelines for the NIEHS Environmental Health Sciences Core Centers program. The major changes would be the institution of a sliding scale for competitive budgets, creation of partner awards to encourage collaborations, and an opportunity fund to encourage resource sharing and cross-training. Reinlib also proposed a term limit for center directors.

The next Council meeting is scheduled for September 10-11.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)



Among several refinements to the EHS Core Centers program, Reinlib proposed some award guidelines that stimulated discussion among members. (Photo courtesy of Steve McCaw)



Shreffler's report on the ONES program was met with extremely positive feedback from Council members. (Photo courtesy of Steve McCaw)

Concepts get green light

Council also approved three concepts during its May 14 proceedings.

Program Administrator Carol Shreffler, Ph.D., presented the proposed revival of the Outstanding New Environmental Scientist (ONES) award program, which seeks to identify and support early stage EHS researchers. The original ONES program, which ran from 2005-2010, made 42 awards in a wide variety of program areas and was considered very successful. The intention is to reannounce the program and make new awards in 2015.

Cindy Lawler, Ph.D., who is acting chief of the Cellular, Organs, and Systems Pathobiology Branch, outlined a proposed new program announcement, Environmental Contributors to Autism Spectrum Disorders. NIEHS has long had an extensive autism research portfolio, and the concept would continue and expand that support, seeking to address gaps in research. The target is to release the announcement in January 2014, with funding to start in December 2014.

Health Science Administrator Heather Henry, Ph.D., who oversees Superfund Research Program (SRP) grants, presented a concept to explore the complex biological, geological, and chemical processes that have implications for exposure risk by living systems. It is anticipated that the announcement would be released this fall, with 6-8 awards being made in the summer of 2014.



David Eaton, Ph.D., of the University of Washington, left, and Tomas Guilarte, Ph.D., of Columbia University, also made their Council debuts at the May meeting. Eaton had many questions and comments during the course of the day. (Photo courtesy of Steve McCaw)



NIEHS Scientific Director Darryl Zeldin, M.D., left and NTP Associate Director John Bucher, Ph.D., conferred during the meeting. (Photo courtesy of Steve McCaw)

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NIEHS career fair showcases career options

By Monica Frazier

The 16th annual NIEHS Biomedical Career Fair took place April 26 on the U.S. Environmental Protection Agency's campus in Research Triangle Park, N.C.

The event, planned and organized by members of the NIEHS Trainees Assembly and the U.S. Environmental Protection Agency's postdoc community, was an opportunity to network with and learn from invited panelists and speakers, visit participating vendors, and get advice about curriculum vitae (CV) and resumes from experts.

This year's career fair was organized with the wide range of attendees in mind, and offered concurrent panel sessions for those following traditional career routes, careers away from the bench, and non-traditional careers for Ph.D. scientists.

Co-chairs [Staton Wade, Ph.D.](#), and [Kymberly Gowdy, Ph.D.](#), were excited about the varied selection of career panels and workshops the planning committee was able to put together this year. "We really highlighted diverse options and, hopefully, let trainees know where they can fit both within and outside of the traditional research field," Wade commented.



NIEHS Deputy Scientific Director William Schrader, Ph.D., welcomed career fair attendees and encouraged networking during the day's events. (Photo courtesy of Steve McCaw)

A motivating keynote

The fair opened with a keynote address by Patricia Beckmann, Ph.D., titled “A Crook in the Road: A Real World Path in Bioscience Entrepreneurship.” She candidly told the audience about her career path, which included academic and industry positions, ranging from technician, to co-inventor of the drug Enbrel, to founder of Biostrategy LLC.

Her presentation was perfectly correlated with the theme of the fair and included details of how she embraced opportunities in different segments of biomedical science, without fear of failure, and sought out challenges to advance her career in entrepreneurship. Failure in a venture, as Beckmann noted, can be utilized as a way to move forward into the future. For many people, she said, “It is best to fail until you succeed.”

Beckmann related entrepreneurship to everyone in the audience, by describing it as an attitude for life. She proposed that everyone is an entrepreneur on some level, whether in the task of determining how to clone a gene more efficiently, or how to get a child ready to go in the morning more quickly. She described all these tasks as levels of opportunity in entrepreneurship.

“My evolution started as a scientist and as an entrepreneur, because I was given opportunity. Opportunity is really important. Look for it and find something that challenges you and your passion,” Beckman said.

Panels and workshops for every interest

Career panels gave attendees opportunities to ask questions of respected members of many different scientific communities, and included sessions on running a successful lab, science policy, contract research organizations, consulting, drug development, program administration, and several other topics. Panelists gave insight into how they broke into their field, what daily life in their position involves, and how attendees interested in a specific path can prepare themselves for that market.

Workshops proved to be very popular among attendees, in such areas as networking, management and leadership skills, the interview process, and knowing an individual’s career value, providing guidance on additional skill sets needed, beyond scientific training, to help get the position desired. Throughout the day, attendees were able to sign up for personal assessments of their CV or resume by career services experts in their market of interest — industry, government, or academic.

Despite the full schedule of events, attendees were given multiple opportunities to network with other participants, panelists, and speakers.



Staton Wade, Ph.D., co-chair of the NIEHS Career Fair Committee, opened the event by emphasizing its theme — career options. (Photo courtesy of Steve McCaw)



Keynote speaker Beckmann candidly spoke to the career fair attendees about her career path, and encouraged the audience to be creative and willing to accept new challenges in their careers. (Photo courtesy of Steve McCaw)

Gowdy summed up the committee’s mission by saying, “We hope that the attendees took away a broad knowledge of what they can accomplish with a Ph.D., and are better able to explore the multitude of career choices available in the biomedical sciences.”

(Monica Frazier, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Mechanisms of Mutation Group.)



NIEHS visiting fellow Anders Clausen, Ph.D., listened to advice during the panel session on “Running a Successful Lab.” (Photo courtesy of Steve McCaw)



Roger Woodgate, Ph.D., right, of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, responded to questions during the “Running a Successful Lab” session. Also on the panel were Alison Harrill, Ph.D., left, of the Hamner Institutes for Health Sciences, and Sue Jinks-Robertson, Ph.D., of Duke University. (Photo courtesy of Steve McCaw)



Dara Wilson-Grant, associate director of the University of North Carolina at Chapel Hill Office of Postdoctoral Affairs, advised attendees in the proper use of networking, while building professional relationships. (Photo courtesy of Steve McCaw)



NIEHS fellow Tracy Clement, Ph.D., led a discussion on “Making the Most of LinkedIn,” in one of the fair’s two lunchtime sessions. (Photo courtesy of Steve McCaw)



Former NIEHS fellow Cynthia Holley, Ph.D., took questions during the panel session on “Contract Research Organizations.” (Photo courtesy of Steve McCaw)



Attendees listened intently, during panel discussions at the career fair. (Photo courtesy of Steve McCaw)



Diane Klotz, Ph.D., former director of the NIEHS Office of Fellows’ Career Development, was a presenter at this year’s career fair. (Photo courtesy of Steve McCaw)



NIEHS program administrator Michael Humble, Ph.D., answered questions during a panel discussion on “Overseeing Science: Program Administration and Grant Management” — one of many sessions offered on nontraditional career paths. (Photo courtesy of Steve McCaw)



Former trainees Thaddeus Schug, Ph.D., left, NIEHS health scientist administrator, and Jana Stone, Ph.D., scientific coordinator at Duke University, were panelists for the program administration and grant management session. (Photo courtesy of Steve McCaw)



The 2013 NIEHS Biomedical Career Fair Committee included trainees from NIEHS and EPA. Shown standing, left to right, are NIEHS trainees Georgette Charles, Ph.D.; Julie Hall, Ph.D.; Bethany Hsia, Ph.D.; Kimberly Wiggins, Ph.D.; Margaret Adgent, Ph.D.; Neal Englert, Ph.D.; Maria Shatz, Ph.D.; Christine Ekenga, Ph.D.; and Michelle Oakes of EPA. Seated, left to right, are EPA trainees Jennifer Nichols, Ph.D., and William Polk, Ph.D.; and NIEHS trainees Wade Gowdy; Wei Qu, Ph.D.; and Rachel Goldsmith, Ph.D. Not pictured are EPA trainee Dayne Filer and NIEHS trainees Jacqueline de Marchena, Ph.D.; Queying (Charlene) Ding; and Bret Freudenthal, Ph.D. (Photo courtesy of Steve McCaw)

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Ethics Day draws capacity crowd

By Eddy Ball

Ethics training programs traditionally present a challenge for organizers. As NIEHS Deputy Ethics Counselor Bruce Androphy, J.D., admitted during the fourth annual NIEHS Ethics Day May 21, “Making ethics fun and interesting is not an easy task.”

Androphy and his team pulled out all the stops again this year, in their quest to turn the discussion of ethics into an event that would attract people from all sectors of NIEHS, for something exciting as well as instructional. As Herculean as that task may have seemed, the members of the Ethics Office succeeded famously.

The team interspersed two hot-topic talks on applied ethics, with seven short and humorous homemade videos, concluding the program with a game of Ethics Bingo that turned the mastery of ethical concepts into a laughter-filled competition. The team also enlisted the musical talent and wit of NIEHS and NTP Director Linda Birnbaum, Ph.D., who has made ethics one of her top priorities at NIEHS.



Birnbaum, right, and Androphy were the perfect combination for an Ethics Day filled with wit and wisdom. As in previous years, a central message of the event is that people need to ask before they act, if there is any possibility of even the appearance of unethical behavior. (Photo courtesy of Steve McCaw)

“This [annual Ethics Day] is a very, very special thing that we do here at NIEHS,” Birnbaum told the audience. “It’s really not done anywhere else that I know of, certainly not at [other parts of] NIH, and we’d love to export it.”

“It’s really a great opportunity for all of us to learn something new to update our knowledge of ethics and bioethics issues,” she said. “At the same time, it’s an opportunity to have some fun and play some ethical games ... [and] I hope most of it you will remember.”

Ethics in the workplace and in society

Before moving into the more serious portion of the program, Birnbaum and Androphy led the audience in an a cappella performance of “Filing Day,” sung to the music of the Beatles’ classic “Yesterday.” Birnbaum’s lyrics offered a humorous take on the ethics requirements and the consequences of failure to comply.

This year’s featured guest speaker was Cheryl Kane-Piasecki, a program analyst in the U.S. Office of Government Ethics (OGE) Training Products Development Section. Kane-Piasecki addressed a “New OGE Game Changer — Service on Professional Boards.”

The presentation outlined **new rules** changing a regulation that, since 1996, has prohibited federal employees from serving in their official capacity on the board of a nonprofit, without a waiver from their agency. The waivers could be difficult to obtain and effectively discouraged employees from accepting positions on everything from scientific panels to neighborhood boards.

According to Kane-Piasecki, although the new rules expand opportunities for agencies to create arrangements for allowing more employees to serve on boards, they in no way release employees from their other ethical obligations in regard to conflict of interest. “I personally think this is a great move,” said Androphy about the new rules, echoing the widespread support for the changes among advocacy groups and federal employees.

With the event’s second presentation by NIEHS Bioethicist David Resnik, J.D., Ph.D., on “Food Ethics: Public Health Versus Human Freedom,” the program shifted focus from the practical workplace issues to philosophical considerations in public policy. Resnik analyzed efforts to legislate better health, by restricting sales of unhealthy food or discouraging poor eating habits through punitive taxation. “How should society balance these competing values [of individual freedom and the greater good of public health]?” he asked.



Kane-Piasecki’s presentation on participation in nonprofit organizations inspired a number of questions from scientists in the audience, who either serve under current regulations or want a chance to serve under the new rules. (Photo courtesy of Steve McCaw)



Resnik used plastic cups as props to show the audience what is legal and what would be banned under New York City’s soft drink rules. He said 60 percent of residents opposed the ban, which is currently suspended by court order. (Photo courtesy of Steve McCaw)



Student Temporary Employment Program staffer Casey Bledsoe emceed Ethics Bingo. (Photo courtesy of Steve McCaw)

According to Resnik, there are no simple answers to the question of when paternalism is justified to protect people from themselves, as in restrictions on junk food to combat obesity; to promote safety for susceptible populations, such as children with peanut allergies; or to guard society against additional healthcare expense, as in motorcycle helmet laws. Age and competency considerations can justify restriction of individual freedom, and, he said, “I think the numbers do matter here.” The more people affected and the more expense involved can be central considerations in which way the regulatory pendulum swings — toward more individual freedom, or toward the greater social good.



Ethics Bingo helped make the educational aspect of the meeting a fun experience. NIEHS Deputy Director of Management Joellen Austin, right, and Chief of the Operations and Security Branch Mitch Williams joined in the fun, as did others in the capacity audience. (Photo courtesy of Steve McCaw)



NIEHS biologists Lisa Padilla-Banks, left, and Justin Kosak shared a laugh as Ethics Bingo challenged the audience with answers to match the prompts on the screen. (Photo courtesy of Steve McCaw)

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Researchers bring environmental health perspective to pediatrics meeting

By Eddy Ball

NIEHS and NTP director Linda Birnbaum, Ph.D., and Institute grantees were plenary presenters at the high-profile Pediatric Academic Societies (PAS) [annual meeting](#) May 4-7 in Washington, D.C. The PAS meeting is the largest international meeting focused on research in child health, attended by some 7,000 pediatricians and academics from around the world.

Birnbaum and Mount Sinai School of Medicine (MSSM) lead researcher [Philip Landrigan, M.D.](#), were featured speakers May 4 at the PAS State of the Art Plenary, “Contemporary Issues in Environmental Health for Pediatricians.” NIEHS-supported environmental scientist [Leonardo Trasande, M.D.](#), of the New York University School of Medicine, was also part of the program.



Birnbaum urged pediatricians to take the offensive, to prevent adverse effects on children’s environmental health. “Educate yourself and others on the major exposures of concern. Ask parents, especially expectant mothers, about their exposures; encourage use of prenatal vitamins, such as folic acid; and counsel parents to avoid prenatal and early life exposures.” (Photo courtesy of Steve McCaw)

University of Cincinnati (UC) lead researcher [Aimin Chen, M.D., Ph.D.](#), presented, as yet, unpublished findings from his group's newest study, "Cognitive Deficits and Behavior Problems in Children with Prenatal PBDE [polybrominated diphenyl ether] Exposure," May 6 in the Academic Pediatric Association Presidential Plenary. As part of the program, one of the members of that group, Simon Fraser University lead researcher and former UC professor [Bruce Lanphear, M.D.](#), received the 2013 American Pediatric Association Public Policy and Advocacy Award.

Framing the conversation about children's environmental health

For traditionally trained pediatricians, children's environmental health is too often a poorly mapped frontier. So it was fitting that Birnbaum's presentation, "Developmental Perspectives on Environmental Stressors and Children's Health," offered a useful primer for the uninitiated and a solid refresher course for the more experienced.

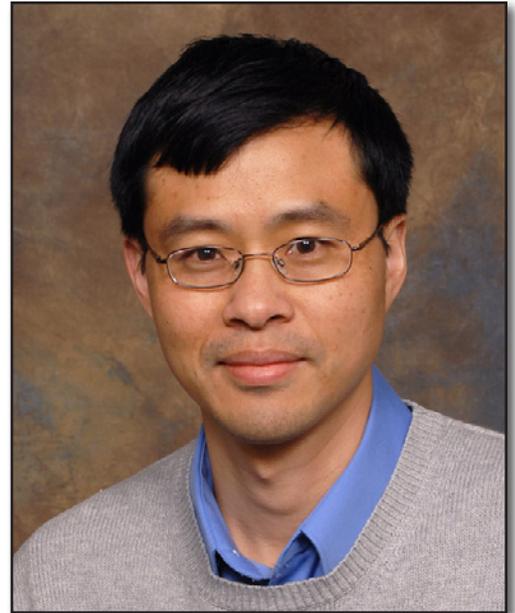
The talk opened with shocking statistics about the decline of children's health, as the number of children with developmental disability or delay continues to grow, up 17 percent in the past decade alone, and even more suffer from asthma and overweight or obesity.

If those trends weren't sufficient cause for concern, Birnbaum added, "Today nearly one-half of children are allergic to something." Paralleling these trends in health is an equally dramatic increase in the many chemicals in the environment that have been linked to those very diseases and health conditions.

As Birnbaum explained, NIEHS has committed enormous support for research, to better understand the effects of environmental exposures on children's diseases, and conditions individuals may not develop until much later in life. She said those adult-onset illnesses, such as diabetes and cardiovascular disease, are increasingly associated with environmental exposures during early-life critical developmental windows of susceptibility.

Fire retardant chemicals and children's neurological health

Research by Chen, Lanphear, and a group of their UC colleagues, in what they call the Home Observation for Measurement of the Environment (HOME) study, represented the most recent evidence of the link Birnbaum had described between early exposure to environmental chemicals and persistent adverse health effects. Chen's group measured levels of fire retardant chemicals from the group of PBDEs used widely in consumer products over the past 30 years. They tested 309 women at 16 weeks of gestation, and evaluated their children over the next five years for cognitive and motor abilities, and behavioral deficits.



In addition to his work with the HOME study, Chen is also regarded as a leading authority on the health effects of electronic waste recycling, a growing environmental health problem in developing countries (see story). As his research has shown, televisions, computers, and other electronics contain a host of hazardous chemicals and metals. (Photo courtesy of UC)



According to PAS, Lanphear's Public Policy and Advocacy Award recognizes his cumulative contributions toward public policy advocacy efforts at the state, regional, national, or international level that have improved the health and well-being of infants, children, and adolescents. (Photo courtesy of UC)

Their findings indicated that higher levels of one of the PBDEs, BDE-47, in maternal serum was associated with neurological deficit. A ten-fold increase over U.S. adult national reference levels translated into a 4.5-point decrement in full-scale intelligence quotient (IQ) at age 5, and a 2.9-point increase in the hyperactivity score at age 2-5 years.

“A four-point IQ difference in an individual child may not be perceivable in ... ordinary life,” Chen was quoted as saying in a *Scientific American* [interview](#) with writer Dina Maron. “However, in a population, if many children are affected, the social and economic impact can be huge, due to the shift of IQ distribution and productivity.”

In her comments for the story, Birnbaum, who is also an authority on PBDEs, conceded that more research is needed to understand the long-term effects of exposure. “We don’t have data [yet] on whether or not the cognitive or behavioral impacts will reverse,” she said. “We know from many other exposures to different kinds of environmental compounds that impact behavior or intelligence that [the impact] doesn’t go away.”

Citation: Chen A, Yolton K, Rauch S, Webster GM, Hornung R, Sjodin A, Dietrich KN, Lanphear BP. 2013. Cognitive Deficits and Behavior Problems in Children with Prenatal PBDE Exposure. Manuscript in prepublication review.

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Landrigan is the director of one of the first sites established as part of the National Children’s Study (see story). His talk, “How Do We Effectively Translate Science to Public Health Policy,” addressed a central issue in the promotion of primary prevention in children’s environmental health. (Photo courtesy of MSSM)

ONES awardee elected to American Society for Clinical Investigation

By Eddy Ball

NIEHS grantee Gokhan Mutlu, M.D., is one of the 80 early career physician-scientists inducted into the [American Society for Clinical Investigation \(ASCI\)](#) for 2013, during its annual joint meeting with the American Academy of Pediatrics April 26 in Chicago.

[Mutlu](#) is an associate professor of medicine at the Northwestern University Feinberg School of Medicine, specializing in pulmonary and critical care medicine, and an associate editor of the *American Journal of Respiratory and Critical Care Medicine*.

As one of the first group of grantees awarded Outstanding New Environmental Scientist support in 2006 ([see story](#)), Mutlu has been conducting research on the effects of fine particle exposure on blood flow and heart disease risk, with a [project](#) titled “Mechanisms of Airborne Particulate Matter Induced Thrombosis,” which was renewed in 2012 for five more years.

As ASCI bylaws stipulate, to be considered for membership, “[A prospective member must be a] physician who is 50 years of age or less [and] has accomplished meritorious original, creative, and independent investigations in the clinical or allied sciences of medicine and enjoys an unimpeachable moral standing in the medical profession.”

“I am honored to have been elected to the American Society of Clinical Investigation, whose mission is to advance medical research,” Mutlu said. In a message to NIEHS program administrators, he also credited his NIEHS grant support. “I believe that the ONES award was the key factor for my election,” he wrote.

ASCI is dedicated to the advancement of research that extends understanding and improves the treatment of human diseases, and members are committed to mentoring future generations of physician-scientists. The ASCI considers the nominations of several hundred physician-scientists from the United States and abroad each year.

ASCI membership includes more than 3,000 physician-scientists from all medical specialties, selected for their outstanding records of scholarly achievement in biomedical research. The membership represents active physician-scientists who are at the bedside, research bench, and blackboard. Many of its senior members are widely recognized leaders in academic medicine.



Mutlu, right, joined members of his lab to share congratulations for the ASCI recognition of their leading-edge research. Shown with Mutlu, left to right, are Scott Budinger, M.D., Micah Rogel, Ph.D., graduate student Saul Soberanes, Luisa Morales, M.D., and Recep Nigdelioglu, M.D. (Photo courtesy of Gokhan Mutlu)

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Former NIEHS STEP student encourages others to dream big

By Robin Arnette

Brian Rogers was happy with his job loading bags at Raleigh-Durham International Airport. While it didn't pay a lot of money, it covered his bills and gave him a chance to figure out what he wanted to do with his life. After seven months of constant lifting, Rogers developed a hernia that forced him to think about a new occupation.

For the next 10 years, Rogers focused on education and his interest in research and medicine. In May 2013, he graduated with an M.D. from Howard University College of Medicine, and this fall will begin a residency in anesthesiology at Duke University Medical Center. As he's done every year since entering medical school, he's at NIEHS doing research for the summer ([see text box](#)).

Rogers' career path took a wonderfully circuitous route, and he wants to inspire others to believe in themselves, too.

Following opportunities

Before his stint at the airport, Rogers, a Durham, N.C., native, majored in business at the University of Utah in Salt Lake City, but dropped out. He didn't take his studies seriously then, but when his medical condition arose, he realized going back to school was his best option.

He applied to North Carolina Central University (NCCU) in Durham, and the school offered him a conditional acceptance. Rogers chose biology as his major and by the end of his first semester ranked at the top of his classes. Impressed with his work, the chairman of the biology department told him about an exciting program.

"NCCU had a co-op program where I worked 20 hours a week at the U.S. Environmental Protection Agency, and the rest of the time I went to school," Rogers said. "It covered tuition and paid me a stipend, which was more than I'd make in a year at the airport."

Rogers completed his bachelor's degree in 2006 with honors, but since he didn't land any positions in his new field, he began a master's degree in biology, specializing in bioinformatics at NCCU. While he enjoyed working with computers, a year later he felt the urge to volunteer a few days a week in a biomedical research lab.

He emailed several scientists at NIEHS and Kenneth Olden, Ph.D., Institute director at the time, wrote him back. Olden also did research and quickly accepted him into the Short-Term Education Program (STEP). Rogers split his time between his master's thesis at NCCU and research at NIEHS.

Realizing his potential

Rogers finished his master's degree in 2009, and was ready to devote all of his time to NIEHS research, but, during his STEP evaluation, Olden did something Rogers didn't expect. He commended Rogers for his exceptional work, but said that he couldn't, in good conscience, hire him because he could do so much more.



Rogers said his long-term goal is to work at an academic medical center, so he can mentor students. (Photo courtesy of Steve McCaw)

Olden believed then, and now, he made the right decision. “I am very proud of Brian and his accomplishments,” Olden said, “because he was willing to do the hard work and make the many sacrifices necessary to become a physician with a strong background in research.”

Interestingly, Olden is married to Sandra White, Ph.D., a professor and Rogers’ academic advisor at NCCU. White fondly recalled Rogers’ analytical thinking skills and the complexity of his master’s thesis, and said, “What I most admire about Brian is his humanity and humbleness.”

NIEHS sharpens Rogers’ research skills

During his time as a STEP student in Olden’s group, Rogers examined arachidonic acid signaling in cell adhesion and migration. Once he became a medical student, Rogers came back, between his first and second years, to study the genes involved in the development and progression of liver cancer with Mark Hoenerhoff, D.V.M., Ph.D., of the NIEHS Laboratory of Cellular and Molecular Pathology.

Between his second and third years, he worked with NIEHS Clinical Research Unit (CRU) Medical Director and Acting Clinical Director Stavros Garantziotis, M.D., characterizing gene expression changes in human white blood cells exposed to nanoparticles.

Now that he’s completed his fourth year of medical school, Rogers is heavily involved in clinical trials taking place at the CRU. He’s doing data analysis and patient recruitment, while also performing physicals and taking histories of clinical trial participants. He said he likes coming back to NIEHS, because his belief of becoming a physician began here.

The importance of mentoring

When Rogers decided he wanted to go to medical school, he contacted NIEHS Scientific Director Darryl Zeldin, M.D., to find out more about the application process. Zeldin became another one of Rogers’ mentors, and not only helped him put together an outstanding application, but also prepared him for the rigors of medical school once he got in.

Rogers said, since he’s benefitted so much from mentoring over the years, he wants to see more mentoring programs that encourage young people to aim high.

“I believe I’ve gotten this opportunity, so that I can help others,” Rogers said. “How many other people are out there just like me?”

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NTP researchers win International Society for Neurochemistry recognition

By Heather Franco

While a trip to Cancun may mean a vacation to many, for scientists in the NTP Laboratory [Neurotoxicology Group](#) at NIEHS, headed by Jean Harry, Ph.D., it marked an opportunity to present their scientific work and

participate in an extraordinary experience with leaders in their field. Biologist Chris McPherson, Ph.D., and visiting fellow Ruben Orihuela, Ph.D., earned places in the highly competitive [International Society for Neurochemistry \(ISN\) Advanced School](#) April 16-20.

Along with some 1,000 scientists, they also attended the biennial meeting of ISN April 20-24, held jointly with the American Society for Neurochemistry (ASN).

As part of their experience at the ISN Advanced School, the members of the Neurotoxicity group presented posters detailing their recent scientific works ([see text box](#)). McPherson's work was honored with a top ISN Advanced School award for poster presentations.



Shown in their lab at NIEHS are members of the Harry Group, left to right, McPherson, Harry, and Orihuela. (Photo courtesy of Steve McCaw)

Rare experience yields valuable opportunities

“Participating in the ISN Advanced School was my most unique science training experience,” said McPherson. This prestigious opportunity provides support and training for 70 graduate students and new Ph.D. scientists in the field of neurochemistry.

“I was ecstatic for both of them to be selected for the school,” said Harry. “It is rare to have two students selected from the same laboratory.” This honor speaks not only to the quality of both junior scientists, but also to the mentoring of lead investigator Harry.

The researchers participated in seminars detailing the current state of the field of glial-neuronal interactions. In addition, they were able to present and discuss their own work in an informal setting. “Because of the small size and international attendance, the school gave me the opportunity to interact with both junior and senior investigators from all over the world in a more intimate setting,” explained Orihuela. The study presented by Orihuela prompted a solicitation for manuscript submission by an editor of a special issue of the *British Journal of Pharmacology*. This confirmed to Orihuela the value of such interactions for visibility of one's work.

Both McPherson and Orihuela were able to make connections that will enhance their future careers. McPherson has aspirations to continue his studies integrating environmental exposures with human health issues. Orihuela strives to bring his cross-disciplinary approach to a research team at a premier university or research center.

Enhancing both their science and career paths

“Participating in these types of activities provides trainees with experiences that will enhance their scientific endeavors and their future career paths,” said Harry. Both McPherson and Orihuela appreciated the opportunity to attend these events.

“Thanks to the support of both Jean and NIEHS, I was able to attend this school and magnificent conference, where I was able to interact with, and present my work to, the leaders in my field,” states Orihuela. “It is great working for a mentor who values and encourages us to take advantage of these types of training opportunities,” confirms McPherson. Both agree it is this focus on overall training that has led to the success of the group.

(Heather Franco, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Reproductive Developmental Biology Group.)

Understanding the role of inflammation following neuronal injury

As Harry explained, “Injury to the neurons of the hippocampus can have detrimental effects on brain function and result in conditions such as Alzheimer’s disease and epilepsy.” To resolve these injuries, specialized macrophages, called microglia, produce inflammatory factors to aid in the repair process. “Microglia exist in two states — pro-inflammatory M1 and anti-inflammatory M2 — which produce a unique set of inflammatory factors,” she said.

Orihuela — characterizing the microglia population

Orihuela sought to better understand these two microglial states using an *in vitro* microglial cell line. Upon differentiation of the cells to the M1 state, he found an increase in the expression of oxidative stress genes, nitric oxide levels, and reactive oxygen species. The cells also showed a decrease in basal respiration and an increase in the acidification rate. Together these results demonstrate a change in the bioenergetic profile of the mitochondria, consistent with increased oxidative stress. These responses were not observed upon differentiation to the M2 state. Thus, these distinctions in mitochondrial bioenergetics of the M1 and M2 microglia may help explain the different phenotypes of these two states.

McPherson — an environmental exposure model of neuronal injury

In his award-winning experiments, McPherson investigated the role of the M1 and M2 inflammatory factors in the repair process following brain injury. He used a model in which the hippocampal toxicant trimethyltin (TMT) was administered to mice. “Exposure to this toxicant in mice causes hippocampal injury similar to Alzheimer’s disease,” McPherson explained. “Using this model system, we are able to examine the contribution and shift of the various M1/M2 states of the brain macrophages.” He found that with the onset of neuronal death and phagocytosis, microglia display an M1 stage of activation, and that a shift to the M2 repair phase was critical for promoting the brain to generate new neurons to replace those lost in the hippocampus. Therefore, each of the stages provided a critical step for the full process, and suggested a shift to the M2 phenotype to facilitate the differentiation of stem/progenitor cells to neurons. He is continuing this work to identify the nature of the trigger for this shift.

Insights into the causes of neurodegenerative diseases

Combining the mechanistic data from Orihuela’s work, with the functional data from McPherson’s research, these studies provide a new understanding of the microglia state following brain injury. “We use TMT as a chemical tool to understand the processes associated with neuroinflammation and adult neurogenesis,” McPherson said. “While TMT is not currently in use in the United States, other countries, such as those on the Asian continent, still use TMT commercially as a polyvinyl chloride heat stabilizer and in biocides.”

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Superfund graduate trainees win foundation support

By Sarah Wilkinson

The careers of University of Arizona (UA) graduate students [Linnea Herbertson](#) and [Corin Hammond](#) gained momentum this spring, with announcements of support by the [National Science Foundation \(NSF\)](#) and the [Achievement Rewards for College Scientists \(ARCS\) Foundation](#). Both Herbertson and Hammond are graduate trainees in the UA Superfund Research Program (SRP), working on doctoral degrees in the environmental health sciences, with a field research focus on phytostabilization of mine tailings at the Iron King Mine and Humboldt Smelter Superfund Site in Dewey-Humboldt, Ariz.

NSF fellowship support for Herbertson

Herbertson received a 2013 NSF Graduate Research Fellowship Program award. As an NSF fellow, she will receive three years of funding support, including stipend, travel, and tuition, and have access to a variety of professional development activities.

“My concern for the environment began when I was a child,” said Herbertson. When she entered graduate school, she joined the environmental microbiology laboratory of [Raina Maier, Ph.D.](#), director of the UA SRP, to combine her scientific interests with her passion for the environment. Herbertson’s research explores whether the bacterial community on the roots of plants grown in mine tailings can aid in the sequestration of toxic metals, as well as act as an indicator of plant health and phytostabilization vitality.

After collecting plants grown in the mine tailings, she images the roots using fluorescent in situ hybridization, to characterize the microbial communities and X-ray fluorescence to analyze metals. “I hope my research will help to further our understanding of the mechanisms of bacteria, root, and metal interactions, to help improve phytostabilization efforts,” Herbertson said.

ARCS scholarship support for Hammond

Hammond received a scholarship from the Phoenix chapter of ARCS for the 2013-2014 academic year. Her award will provide tuition, travel funds, and a stipend.

Hammond is a doctoral student training in the environmental chemistry lab headed by UA SRP lead researcher [Jon Chorover Ph.D.](#) Her graduate work is focused on characterizing the biogeochemical transformation of metal(loid)s during phytostabilization of mine tailings.



An avid cyclist, Herbertson often rides by the extensive mine tailings south of Tucson, Ariz., near Green Valley. “On especially windy days, I smell and taste the tailings in the air blowing from the piles,” she said. “Such experiences leave me wondering — how does one address this issue?” (Photo courtesy of Linnea Herbertson)



For Hammond, environmental advocacy is in the blood. She grew up in Corvallis, Ore., a town she describes as particularly environmentally aware. Hammond plans to complete her doctorate in December 2014. (Photo courtesy of Corin Hammond)

“Phytostabilization is complicated by the inhospitable environment the mine tailings provide to germinating plants,” Hammond explained. High acidity, high heavy metal content, and low organic matter content are among the factors that complicate the phytostabilization process. To assess the changes in biogeochemistry associated with the phytostabilization strategy, members of Chorover’s lab analyze soil cores, by laboratory and synchrotron X-ray techniques, to investigate contaminant transport and soil genesis as a function of time and depth.

“I am so fortunate to be selected by the ARCS Phoenix chapter to receive this financial support. It is an inspiration to see our community leaders finance higher education and research that leads to a more sustainable future,” Hammond said of her award.

(Sarah Wilkinson, Ph.D., is the research translation coordinator for the UA SRP, who writes and edits the UA SRP News and Highlights.)

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Grantees honored for breast cancer risk communication

By Eddy Ball

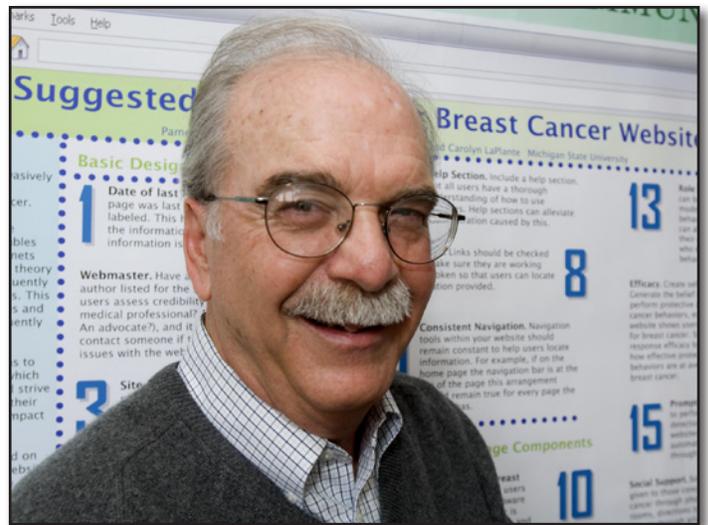
Three members of the NIH-funded Michigan State University (MSU) Breast Cancer and the Environment Research Program (BCERP) are winners of the 2013 [International Communication Association \(ICA\)](#) Applied Research Award. Lead researcher Charles Atkin, Ph.D., and co-researchers Sandi Smith, Ph.D., and Kami Silk, Ph.D., shared honors for their applied communication accomplishments, translating emerging environmental health science research findings into the reduction of breast cancer risk among women of all ages, at every level of society.

In its announcement of the award, the international nominating committee praised the MSU researchers for their public health impact. “Their research is highly productive in several important senses, with an integrative character that embraces multiple scientific disciplines, associated practitioners, and relevant political leaders.”

Public health impact

“The public visibility of the project correlates with its capacity to get public funding and refunding,” the members wrote. “The committee therefore celebrates the research program of Atkin, Smith, and Silk to be a true model for applied communication research, with expansive intellectual and practical impacts.”

Smith and Silk will accept the team’s award June 18, during an awards banquet at the ICA 63rd annual conference in London. Atkin, chairman of the MSU Department of Communication, who died in August 2012, will be remembered June 20 at a special session of the conference, “In Memoriam: The Legacy of Charles K. Atkin.”



In light of Atkin’s death last year, “It is somewhat bittersweet,” wrote Richard Schwartz, Ph.D., in the university’s announcement of the award. Schwartz is associate dean for graduate academic and student affairs for the College of Natural Science at MSU. (Photo courtesy of MSU)

“This award is a tribute to Chuck and his team, and a well-deserved recognition of our program’s commitment to prevention of breast cancer,” said NIEHS program director Les Reinlib, Ph.D., who administers the [BCERP](#) grants portfolio. “Environment has a clear role in breast cancer and a key to preventing it. Communicating with girls and women to understand their perceptions, and send practical messages on avoiding exposure to reduce risk, is the best medicine.”

The MSU Community Outreach and Translation Core (COTC)

The [MSU COTC](#) is comprised of community advocates and faculty members from the Department of Communication, working together to increase awareness about breast cancer, based on state-of-the-science evidence. “We need to help women and children of all ages and backgrounds, to not only access breast cancer information, but to also understand and act on it,” Atkin wrote of the team’s mission.

Among its efforts is an educational and fundraising program known as Meal Patterning for Breast Health, which was organized and implemented by community advocates in coalition with other university and community sponsors. The team has also conducted ten focus groups across four counties in Michigan, to gain an understanding of adolescent and adult female perceptions and understanding of breast cancer and the environment.

COTC staff members are currently piloting a random phone survey across Michigan, to further formative research. This information will help in developing tailored health messages to target various audiences, particularly adolescent females. Looking to the future, MSU has a project website under construction that will explain BCERP activities, as well as provide another source for breast cancer information.

According to organization President [Cynthia Stohl, Ph.D.](#), ICA, which began more than 60 years ago in the U.S., has evolved into a leading international academic association with more than 4,300 members in 80 countries. Since 2003, ICA has been officially associated with the United Nations, as a nongovernmental organization.

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NIEHS fellow launches a career in science administration

By Aleksandra Adomas

Ashley Godfrey, Ph.D., completed her four-year postdoctoral training in the NIEHS Laboratory of Molecular Carcinogenesis and, in May, joined the Duke Cancer Institute as a scientific review officer. In her new role, Godfrey will review oncology clinical research protocols, involving human subjects, for scientific merit and appropriateness.



Smith is director of the Health and Risk Communication Center and a professor in the Department of Communication at MSU. (Photo courtesy of MSU)



Silk is an associate professor in the Department of Communication and the director of the Master’s Program in Health and Risk Communication at MSU. (Photo courtesy of MSU)

Clinical research interest

Godfrey's interest in clinical research, and desire to impact people's health, accompanied her through her education at Louisiana State University and the University of North Carolina at Chapel Hill. Her undergraduate work was centered on plant metabolism, while as a graduate student she focused on basic research and microRNA processing.

She then joined epidemiologist and physician scientist [Jack Taylor, M.D., Ph.D.](#), NIEHS Molecular and Genetic Epidemiology Group lead researcher, to embark on the quest to understand the role of microRNAs in breast and lung cancer.

Working in the Taylor lab offered Godfrey a number of unique opportunities to work in other scientific areas that she would not have had access to otherwise. For example, Godfrey's breast cancer project used samples collected in the NIEHS [Sister Study](#), and looked into the potential of using microRNAs for early diagnosis or as susceptibility markers. Involvement in the study, which includes 50,000 participants, gave her an epidemiological perspective and a chance to design big projects, with hundreds of samples requiring high-throughput processing and advanced analysis. Godfrey also credits her mentor with giving her the freedom and tools necessary to be successful in designing and implementing such large-scale projects.

"I'm happy to see my scientific background in cancer coming together with my clinical interests," explained Godfrey about her enthusiasm for her new position. "I'll be really excited to see all the cutting-edge research and new protocols that might lead to new cancer treatments that can change people's lives."

Diligent job search

At first, Godfrey made regulatory affairs the focus of her job search. "I felt it was a field that could play at my strengths. I'm well organized and I thrive when there's a lot going on at once," she said. To further explore that option, she signed up for the workshop series preparing for the Regulatory Affairs Certification (RAC). The classes, organized by the North Carolina Regulatory Affairs Forum ([NCRAF](#)), turned out to be a great source of information and a valuable networking opportunity. The theoretical knowledge acquired in the classroom, combined with the practical experience gained during an internship at the Duke Translational Medicine Institute and topped off with a lot of studying, helped Godfrey pass the RAC exam.

Adding the RAC certification to her long list of qualifications resulted in many job interviews, on the phone and in person, but lack of industry experience dissuaded potential employers. Still, credentials gave Godfrey confidence in answering interviewers' questions and boosted her perseverance in the job search.



Godfrey's advice to all the trainees was to attend as many networking and educational events, as well as lunches hosted by local organizations and societies, as possible. "It's not easy to talk to people at first, but you tend to get the same questions and, with practice, it gets easier," she said. (Photo courtesy of Steve McCaw)



"Doing a fellowship in my group helped Ashley build her knowledge of the clinical and epidemiologic aspects of biomedical research that was important for her getting the job at Duke," Taylor said. "That interdisciplinary research experience, coupled with her drive to network, develop, and explore multiple career paths was key. I think it's a great match for her." (Photo courtesy of Steve McCaw)

Networking led Godfrey to many of the positions that she applied for, and others were advertised online. The scientific review officer job ad caught the eye of a friend who then sent it to Godfrey. Through contact with former NIEHS trainee Brant Hamel, Ph.D., currently at Duke Cancer Institute, she found out the name of the hiring manager and then approached him directly.

Godfrey took full advantage of the career support available to the NIEHS postdoctoral fellows, by attending workshops, seminars, and brown bag lunches; meeting with the NIH Office of Intramural Training and Education Career Counselor, Denise Saunders, Ph.D.; and regularly contributing to the Environmental Factor newsletter. Godfrey was also active in popularizing available career choices, by co-chairing the 2012 annual NIEHS Biomedical Career Fair and serving on the fair planning committees in 2010 and 2011.

(Aleksandra Adomas, Ph.D., is a research fellow in the NIEHS Laboratory of Molecular Carcinogenesis.)

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Trainee meeting focuses on workforce trends

By Eddy Ball

As the annual general meeting of the [NIEHS Trainees Assembly \(NTA\)](#) May 10 underscored, career development is more important than ever in today's market, as budget cuts and trends in the biomedical workforce are bringing changes to the training and career experience.

The meeting opened with a short presentation by NTA Steering Committee Co-chair [Anne Marie Jukic, Ph.D.](#), on big-picture trends in the biomedical workforce that reinforced the title of her first slide, "Why you should care."

The program moved seamlessly into the featured presentation by NIEHS Scientific Director [Darryl Zeldin, M.D.](#), on the Institute's budget for the remainder of fiscal year (FY) 2013 and projections for FY 2014 that directly impact the NIH biomedical workforce. "There's no way to sugarcoat [these developments]," Zeldin told the audience. "There's really no good news here.... [But] fortunately, we planned ahead."

Following Zeldin's talk was a presentation by NIEHS Division of Extramural Research and Training Program Administrator [Michael Humble, Ph.D.](#), on changes to an important NIH grant mechanism, known as [K99/R00](#), that provides generous mentoring and early career support for trainees who



Even before his appointment in October 2011, Zeldin was aware of the need to prepare for anticipated cuts. His response to the possibility of fiscal restraint is a major reason why there have been no layoffs in the Division of Intramural Research, which, like other NIEHS divisions, now has to do its job with diminished resources. (Photo courtesy of Steve McCaw)



With his sobering report on the NIEHS budget, Zeldin had the undivided attention of the trainees. While the meeting was well attended, the turnout reflected the reduction in the number of trainees currently at NIEHS. (Photo courtesy of Steve McCaw)

are successful with their applications. Two trainees received K99 awards this year — one from the Mitochondrial DNA Replication Group and one from the Chromosome Stability Group.

Concluding the program, Director of the NIEHS Office of Fellows' Career Development (OFCD) [Tammy Collins, Ph.D.](#), outlined career development workshops and classes scheduled for the upcoming academic year.

Looking at disconcerting trends at NIEHS and nationwide

Jukic's slides highlighted two trends in the biomedical workforce. The first showed a growth in the number of scientists with doctoral degrees, which nearly doubled from 2009 to 2011. The second offered estimates of the percentage of jobs closely related to training, which fell from almost 71 percent to just over 59 percent during the same period.

According to Jukic, those figures translate into a compelling argument for trainees to develop a complementary skill set, with communications at the top of the list, to empower them in both traditional and off-the-bench employment.

Zeldin's figures on employment at NIEHS, which mirror trends at other institutes and centers, were also grim. But unlike workforce trends, over which NIEHS leadership had no real control, Zeldin and other senior officials at NIEHS were able to plan in advance, so that most of the Institute's budget cuts have been absorbed through attrition and spending freezes. The number of lead researchers has dropped by nearly 25 percent since 2008, he said, and the number of trainees is down by more than 30 percent.

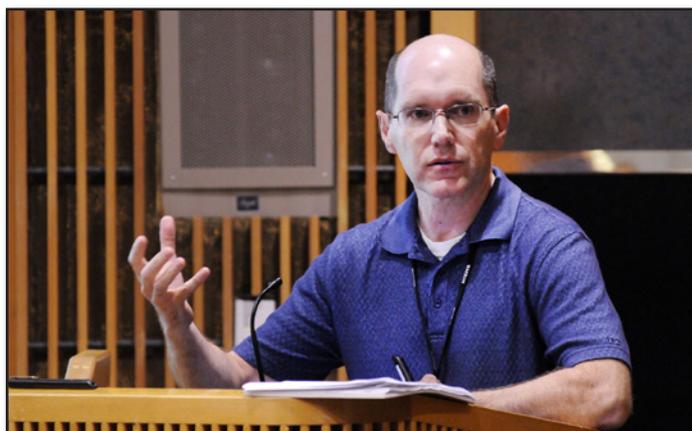
Looking back, philosophically, on the ebb and flow of the biomedical workforce in past decades, Zeldin said, he was cautiously optimistic about the long term. "Ultimately, things will be better," he told his younger colleagues.

(Re)visioning the training experience

Following Humble's presentation (see text box), Collins returned to Jukic's theme of developing additional skill sets to complement training in the lab.



Jukic, right, joined Zeldin for questions from the audience. Their presentations reinforced the message that trainees need to take control of their career development, as early as possible in the training cycle. NTA Steering Committee Co-chair [Rachel Goldsmith, Ph.D.](#), joined other presenters in the front row. (Photo courtesy of Steve McCaw)



Humble urged trainees trying for K99/R00 mentoring and early career support to start looking two years out, and apply early enough to take advantage of opportunities for revising their applications. (Photo courtesy of Steve McCaw)



The presentations were especially relevant for senior trainees, such as [Jim Aloor, Ph.D.](#), left, who are getting closer to their transitions into employment. (Photo courtesy of Steve McCaw)

Along with a broad range of NTA resources, such as the annual Biomedical Career Fair ([see story](#)), and internship experiences in communications and outreach teaching, OFCD organized 11 workshops over the 2012-2013 academic year for helping trainees grow their career development skill set, with training in grantsmanship, management, and other areas, including an upcoming event June 7 on interviewing and negotiating. Collins encouraged trainees to take advantage of the NIEHS LinkedIn group and regular opportunities for career advising by the NIH Career Counseling Center.



Collins listened as people asked questions. She was prepared with a variety of career development opportunities, to help trainees prepare to enter the changing biomedical workforce. (Photo courtesy of Steve McCaw)

Collins told trainees to expect a comprehensive survey in their email boxes and urged them to let her know what else they need in the area of career development. As she talked about her commitment to make sure NIEHS trainees benefit from resources available through the NIH [Office of Intramural Training and Education](#) in Bethesda, Md., Collins also encouraged the audience to craft individual development plans, as early as possible during their time at NIEHS, taking advantage of resources at <http://myidp.sciencecareers.org>.

Early career support grants – changes in timing and provisions

Humble opened his report on upcoming changes to the K99/R00 grant program, with a reference to the NIH Advisory Committee to the Director [Biomedical Workforce Task Force](#) report. Noting that the time to degree, and time to first grant, had increased for trainees over the years, Humble posed the question on the minds of many who have looked at workforce trends. “How can we speed up the training process?”

One way, it turns out, is to implement a change in the eligibility application window, which will be effective in February 2014. At that time, the eligibility for applying will be limited to four years of training, rather than five.

This change in timing is important, Humble explained, because the new K99 provisions require no fewer than 12 months of mentored training and career development, prior to award of early-career research support, the R00 portion of the award. Applicants who fail to complete the year of mentored training and career development will sacrifice the R00 part of the coveted award.

“The idea is to get the award to you earlier,” Humble said. He added that administrators are aiming for a 30 percent success rate under the new provisions. He also reminded the audience that the K99/R00 program awards grants to trainees who are noncitizens as well as citizens.

Zeldin reminded attendees that a new NIEHS program, initiated last year, rewards trainees with a \$2,000 merit increase to their training stipend for a successful K99/R00 application ([see story](#)), and gives their lead researchers an additional training position in their labs.

UW centers co-host Duwamish River Superfund cleanup forum

By Sara Mishamandani

The University of Washington (UW) hosted approximately 70 attendees for an educational workshop April 29 in Seattle, to discuss the U.S. Environmental Protection Agency (EPA) [Duwamish River Superfund cleanup proposal](#). Organized by the UW [Superfund Research Program \(SRP\)](#) and the [Center for Ecogenetics and Environmental Health \(CEEH\)](#), the meeting was part of the Duwamish River Cleanup Coalition's outreach plan to educate the university community about the cleanup during the public comment period, and it marked the most recent of three collaborative efforts between the UW SRP and the CEEH.



Participants of the workshop listened intently to panel presentations. (Photo courtesy of Jon Sharpe)

 **Linked video:**
[Watch a series of seven short videos of presentations at the meeting](#)
(Launches in new window)

Download Media Player:  Flash 

The meeting included students and staff from Seattle Pacific University and UW; a Duwamish tribal member; EPA staff; the Washington State Department of Ecology; the City of Seattle, representing the Lower Duwamish Waterway Group; and the Duwamish River Cleanup Coalition/Technical Advisory Group (DRCC/TAG).

Representatives from each group presented their perspectives on the EPA proposal for cleanup of the Duwamish River. After hearing from several stakeholders, meeting participants were encouraged to submit [public comments](#) by June 13, to provide input for the EPA cleanup proposal.

The cleanup effort

In 2001, a 5.5-mile stretch of the lower Duwamish River was declared a federal Superfund site. More than 40 different toxicants contaminate the river, mostly in the river bottom sediment, including polychlorinated biphenyls, dioxins and furans, carcinogenic polycyclic aromatic hydrocarbons, and arsenic.

Because of contamination, state and local health departments warn against eating crab, shellfish, or bottom-feeding fish from the river. However, the waters in and around the site are used by the Muckleshoot and Suquamish Tribes, as part of their usual and accustomed fishing areas. According to spokespersons, the well-being of these tribal members, and others living nearby, are intimately tied to the health of the river.



UW COEC director [Kelly Edwards, Ph.D.](#), moderated the event. (Photo courtesy of Jon Sharpe)

EPA estimates the cleanup proposal will reduce the risk associated with eating contaminated fish and shellfish by 90 percent. The proposed plan includes dredging to remove contaminated sediment, pursuing natural recovery of contaminated sediment by covering it with six or more inches of clean material, and monitoring the river's recovery. DRCC/TAG, the EPA official community advisory group, developed a comprehensive set of recommendations to the EPA plan, which are highlighted in the latest [UW SRP e-bulletin](#).

Other outreach activities

As part of the effort, UW toxicologist [Evan Gallagher, Ph.D.](#), presented information about his NIEHS-funded Superfund research during a tour of the Lower Duwamish River Superfund site, as part of the NIEHS Environmental Health Science (EHS) Core Centers meeting April 17-19 in Seattle ([see story](#)). Gallagher's UW SRP project focuses on mechanisms of metal and pesticide-induced olfactory injury in salmon, and applications in Superfund site biomonitoring. In May, his student, Chase Williams, described his research findings on fish behavior and responses to cadmium as part of an [SRP Trainee Webinar](#).

The UW SRP also worked alongside the CEEH Community Outreach and Ethics Core (COEC), to support a Public Health Café April 18 for the Seattle community, during the EHS Core Centers meeting.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

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Allison Hiltner, EPA's manager for the Duwamish cleanup, second from right, answered questions following the presentations. (Photo courtesy of Jon Sharpe)

Postdocs showcase outreach program at local school

By Eddy Ball

Members of the NIEHS community turned out May 2 to show their support for outreach efforts by Institute trainees at Lowe's Grove Middle School in Durham, N.C.

Linked video:
[Watch a video about the debut Citizen Schools program at Lowes Grove \(03:05\)](#)
(Launches in new window)

Download Media Player: Flash



Lao, left, and Reid enjoyed some time together, as the NIEHS spring outreach and science education program at Lowe's Grove came to a successful conclusion. (Photo courtesy of Steve McCaw)

The WOW! Event marked the conclusion of the spring 2013 program, conducted by NIEHS postdocs as part of the [Citizen Schools North Carolina](#) effort in Durham and Charlotte schools. It was a time for families, friends, and members of the community to celebrate the achievements of their young students' ten weeks of extracurricular learning about science, technology, and other professions.

The programs at Lowe's Grove, and other schools nationwide, are presented by what the Citizen Schools organization calls citizen teachers, as part of a grass-roots campaign to ground education in a real world context, to nurture the next generation of America's workforce. With support from the NIEHS [Office of Science Education and Diversity \(OSD\)](#), early-career scientists from the Institute volunteered scores of hours, both at work and home, in preparation for ten weeks of enrichment for the students, in a series of learning activities related to respiratory health.

Along with expanding student awareness of science itself, explained outreach program coordinator Huei-Chen Lao, "The program brings scientists very near to the students, to show that scientists are just normal people with a passion for learning about the world around them." Interacting with young scientists, agreed OSD Director Ericka Reid, Ph.D., presents students with approachable models for who they could be, if they decide to pursue careers in science, technology, engineering, or mathematics (STEM). That relationship is reflected in the term "apprentice," which is how the Citizen Schools program describes its student participants.

Building on the past, looking to the future

NIEHS involvement in the Citizen Schools program at Lowe's Grove began in 2011, with trainee-initiated planning for the spring 2012 "Healthy Lungs, Happy Living" apprenticeship ([see story](#)), the largest volunteer apprenticeship ever at Lowe's Grove. The program was so successful that Citizen Schools was eager to host the NIEHS respiratory health curriculum again this spring.

Planning for the fall program has started already, with Institute postdocs developing a new curriculum in cell biology. Several volunteers from the spring program have already made a commitment for the next session beginning in September. [Lao](#) encourages postdocs, scientists, and other NIEHS employees, with an interest in outreach and teaching, to join current volunteers at Lowe's Grove in the fall.



NIEHS Deputy Director [Rick Woychik, Ph.D.](#), center, was on hand to learn about, and experience, each of the four team exhibit experiments from interns in lab coats. Standing behind him, left, is Laboratory of Molecular Carcinogenesis fellow [Kimberly Wiggins, Ph.D.](#) (Photo courtesy of Steve McCaw)



NTP biologist [Pamela Ovwigbo](#), second from right, brought along her son for a little hands-on introduction to respiratory health. Before long, he was enjoying himself, as he took apart the lung model for a closer look at the sections of that all-important organ. (Photo courtesy of Steve McCaw)

Career development as a labor of love

For the nearly 30 postdocs who have been a part of the NIEHS Citizen Schools program, outreach is an opportunity to pay back, pay forward, and invest in careers. In addition to nurturing young minds, as they were nurtured by their own mentors, and promoting scientific literacy for the next generation, volunteers are adding experience to their resumes that will help them stand out in job searches to come.

“It’s a great opportunity to share what we love,” said Laboratory of Structural Biology visiting fellow [Sara Andres, Ph.D.](#), “to get younger students interested in science, so one day they can do the same thing.” An important part of what motivates the volunteers is to help advance STEM careers, overall.

“One of the reasons I was interested, was because I wanted to see what the U.S. school system is like,” explained Laboratory of Signal Transduction visiting fellow [Felicity Davis, Ph.D.](#), a native of Australia, who added that she’s ready for more involvement with the program. “Sara and I are both signed up for the next time [the fall cell biology internship].”

“I plan to use this on my CV as an initial teaching experience,” Andres added. “I know they’re younger, but teaching is teaching at all levels.”

Volunteers from NIEHS

Contributing to this year’s effort are a lucky 13 trainees from research groups across the Institute:

- Margaret Adgent, Ph.D.
- Sara Andres, Ph.D.
- Miranda Bernhardt, Ph.D.
- Lindsay Buckley, Ph.D.
- Christopher Campos, Ph.D.
- Felicity Davis, Ph.D.
- Jacqueline de Marchena, Ph.D.
- Yanshun Liu, Ph.D.
- Caroline Pantazis
- Wipawee (Joy) Winuthayanon, Ph.D.
- Shannon Whirlledge, Ph.D.
- Kimberly Wiggins, Ph.D.
- Taylor Wolfgang



NIEHS Office of Fellows’ Career Development Director [Tammy Collins, Ph.D.](#), center; and her husband, John, joined in the fun, as she showed her support for the fellows’ outreach work in local schools. (Photo courtesy of Steve McCaw)



For the students, who had worked with their own teams to get projects ready for the big night, part of the fun was checking out the other displays. (Photo courtesy of Steve McCaw)



As the NIEHS volunteers broke down their displays to make room for another group, Reid, left, and Collins joined Citizen Schools North Carolina liaison Joshua Johnson and Senior Campus Director Jin Ellington. (Photo courtesy of Steve McCaw)



Volunteers showed off the “Health Lungs, Happy Living” poster, as they prepared to pack up equipment for the trip back to NIEHS. On hand the big night, left to right, were Davis; Epidemiology Branch fellow [Margaret Adgent, Ph.D.](#); Andres; Laboratory of Reproductive and Developmental Toxicology fellow [Miranda Bernhardt, Ph.D.](#); Wiggins; and Lao. Not shown: Laboratory of Reproductive and Developmental Toxicology research fellow [Wipawee \(Joy\) Winuthayanon, Ph.D.](#) (Photo courtesy of Steve McCaw)

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Science Notebook

Katsuhiko Mikoshiba delivers 2013 Rodbell Lecture

By Sheila Yong

The prestigious Dr. Martin Rodbell Lecture Series Seminar April 30 went international this year with Katsuhiko Mikoshiba, M.D., Ph.D., as its fifteenth speaker. In his talk on the “Role of IP3 receptor signaling in development, cell function, and diseases,” Mikoshiba discussed how he discovered the inositol 1,4,5-triphosphate (IP3) receptor, and his ongoing quest in characterizing the protein.

Mikoshiba is currently the senior team leader of the developmental neurobiology team at RIKEN Brain Science Institute.

Host James Putney, Ph.D., head of the NIEHS Calcium Regulation Group in the Laboratory of Signal Transduction, compared Mikoshiba’s scientific career with that of Rodbell. “Dr. Mikoshiba’s career path is very similar to that of Dr. Rodbell in that both of these scientists made an observation very early on that they did not initially understand. Nonetheless, with relentless dedication, they subsequently developed them into the definition of the entire field of biomedical research.”

The discovery of IP3 receptor

When IP3 was first shown to trigger calcium release from inside the cells, many researchers, including Mikoshiba, became interested in determining how this release is regulated. “Calcium ions, though essential for normal cell function, are detrimental when present at excessive levels,” he explained. “Therefore, understanding how the internal calcium levels are regulated is important for determining how certain abnormalities that affect calcium signaling result in disease.”

Mikoshiba stayed with what he knows best — the brain. While a postdoctoral fellow with Jean-Pierre Changeux, Ph.D., he had observed that mice lacking the P400 protein exhibited severe defects in the development of Purkinje cells, one of the largest neurons in the brain. As a result, these mice suffered from an inability to coordinate muscle movements.



Mikoshiba said it has been more than 20 years since his last visit to the NIEHS, and he was excited to meet with researchers and some of his longtime friends to exchange research ideas. (Photo courtesy of Steve McCaw)



Rodbell’s widow and honored guest, Barbara, center, has attended every Rodbell lecture. Seated with her is NIEHS and NTP Director Linda Birnbaum, Ph.D., left, who complimented Mikoshiba for his clear and coherent presentation. (Photo courtesy of Steve McCaw)

As a young principal investigator at the time, with only two lab members, Mikoshiba spent more than two years screening for the ideal antibody for detecting P400. This approach proved fruitful because the group was able to use this antibody to purify endogenous P400 and determine its sequence. Furthermore, they also observed that P400 binds IP3. These observations came around the time when IP3 was discovered as a messenger molecule that relays signals from cell-surface receptors to the intracellular environment.

Their results, together with published observations that calcium signaling is absent in Purkinje-cell-deficient mice, led Mikoshiba's team to conclude that P400 is the bona fide IP3 receptor that also functions as an intracellular calcium channel. Using various techniques in biochemistry, molecular biology, and microscopy, they were able to verify the receptor function *in vivo*, and demonstrate its localization at the endoplasmic reticulum where the intracellular calcium stores reside.

The multi-faceted function of IP3 receptor

Since then, Mikoshiba has successfully identified three isoforms of IP3 receptor. Years of research by his team revealed that each isoform regulates a subset of cellular mechanisms, such as cell division, neuronal development, digestive functions, and protection against cellular stress. Therefore, it is not surprising that defects in the receptor or its expression result in a variety of health complications, including Huntington's disease, Sjogren's syndrome, and various autoimmune diseases.

Mikoshiba explained that while the IP3 receptor isoforms have similar protein sequences, they undergo modifications at different sites. The presence of several isoform-specific amino acids further distinguishes these isoforms from one another. "This could explain why the receptor is able to control such a broad spectrum of cellular activities," he said. These distinctions are important in regulating IP3-binding affinity and channel opening, he added.

Analysis of the three-dimensional structure of IP3 receptor also revealed the presence of multiple cavities near the channel pore, rendering it a platform to which many downstream molecules can bind. Mikoshiba referred to it as a signaling hub that facilitates the interaction among various proteins and molecules in different cell types. "The different combinations of proteins that bind to the IP3 receptor help convert a simple IP3 wave into multiple downstream signals, which in turn regulate different cellular functions," he concluded.

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction.)

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With his Rodbell statue in hand, Mikoshiba joined, left to right, Putney, Rodbell, and Birnbaum. (Photo courtesy of Steve McCaw)



Speakers in the Dr. Martin Rodbell Lecture Series receive a statue depicting the hand of Nobel laureate and former NIEHS Scientific Director [Martin Rodbell, Ph.D.](#), holding the three key elements involved in cell signaling. Sculptor Carl Regutti, who created the statue and attended the Rodbell lecture in 2012 as a family guest, died in April of this year. (Photo courtesy of Steve McCaw)

Davidian explores the role of statistics in personalized medicine

By Robin Arnette

Determining the optimal treatment strategy for an individual patient, or personalized medicine, has generated a huge amount of interest during the last 10 years. Much of the attention grew from the hope that a better understanding of the human genome would lead to targeted medical treatments. But, according to biostatistician Marie Davidian, Ph.D., better statistical methods must be developed before doctors and patients reach that goal.

NIEHS Biostatistics Branch Chief Clarice Weinberg, Ph.D., hosted [Davidian](#), when she came to campus May 8 as the featured speaker for the 2013 Distinguished Lecture Series. Davidian is a William Neal Reynolds Professor in the Department of Statistics at North Carolina State University (NCSSU). During her talk, she focused on the role statistical methods will need to play in developing personalized treatment strategies.

Davidian began her seminar by encouraging the audience to expand its definition of a medical treatment.

“We normally think of a [prescription] drug when we think of a treatment, but it could be a biologic, medical device, surgical procedure, or a behavioral intervention,” Davidian said. “Everything from cholesterol medication and an artificial limb, to chemotherapy and cognitive therapy, could be considered a treatment.”

Clinical trials — the gold standard for evaluation

Davidian said, the U.S. Food and Drug Administration evaluates treatments, before they enter the market, by testing a product’s safety, efficacy, and effectiveness. Surprisingly, it wasn’t until 1969 that congressional legislation mandated the use of clinical trial evidence for regulatory approval of a new treatment product in the U.S.

Today, two controlled, randomized clinical trials are required for final treatment approval, and it’s at this juncture that statisticians are most needed. Davidian maintained that the assessment of effectiveness, evaluated through standard statistical methods, boils down to the comparison of average outcomes between, or among, treatments. For example, if clinicians are testing treatments A and B, the classical analysis asks whether the average outcome for all of the patients who took treatment A is different from, and better than, those who took treatment B.



“2013 is the international year of statistics, so I encourage you to visit the [Statistics2013 website](#), because there is a treasure trove of information about the profession,” Davidian said. “Organizers from the five major statistical societies built the site and have done a tremendous job in promoting the discipline.” (Photo courtesy of Steve McCaw)



Weinberg said, “As current president of the American Statistical Association, she [Davidian] is communicating the need to let solid statistical principles guide our efforts in turning big data into actionable inferences.” (Photo courtesy of Steve McCaw)

While comparison of average outcomes might be sufficient for regulatory purposes, knowing that one treatment is better, on average, than another may not be too informative for treating individual patients. Genetics, physiological, and demographic characteristics; previous medical history; and current health status influence response, and this heterogeneity dictates that each patient may require a slightly different treatment. Davidian said, researchers are thus often interested in identifying subgroups of patients that share certain characteristics, such as a specific gene mutation, who may benefit from being treated a certain way.

Identifying a treatment regime

Davidian said that, in clinical practice, physicians use their judgment to identify the appropriate treatment from a number of available options. She and others use statistical research to optimize that process, by developing sets of evidence-based rules, called treatment regimes, that guide doctors in their treatment decisions ([see text box](#)).

She also described recent work that used data from participants in a single study, who received treatments at two or more key decision points in the disease process, to develop optimal treatment regimes. Clinical trials, known as sequential, multiple assignment, randomized trials (SMART), are ideal studies for collecting such data. In SMART trials, patients are randomized at each decision point to receive one of the possible treatment options.

Davidian and other colleagues at NCSU, the University of North Carolina at Chapel Hill Department of Biostatistics, and Duke University Department of Biostatistics and Bioinformatics, have joined forces to develop statistical methods to identify the best treatment regimes for cancer. With funding from the National Cancer Institute, this collaboration will determine how to design multiple randomized trials to collect the information necessary for personalized medicine.

As a biostatistician, Weinberg understands the importance of statistics in handling the enormous amount of information that can be produced by clinical trials. She sees Davidian's contribution as crucial to developing a better understanding of how to treat chronic disease.



NIEHS Developmental Neurobiology Group lead researcher Patricia Jensen, Ph.D., right, and Deputy Scientific Director William Schrader, Ph.D., attended the talk. During the question and answer session, Schrader asked if medicines that have previously failed other clinical trials are being re-evaluated to determine if they work for a certain subgroup of patients. (Photo courtesy of Steve McCaw)



Having analyzed data from several clinical trials, Michael Fessler, M.D., right, of the NIEHS Laboratory of Respiratory Biology was particularly interested in Davidian's lecture. (Photo courtesy of Steve McCaw)

Employing statistics to find the best treatment

The rules that comprise a treatment regime correspond to each decision point in the disease process. As an example, Davidian gave the following hypothetical rule for the use of induction chemotherapy in breast cancer patients.

She said, “Suppose there are two options, which I’ll call chemotherapy 1 (C1) and chemotherapy 2 (C2). If the age of the patient is less than 50, and the progesterone receptor (PR) level is less than 10, give C1, otherwise C2.”

Davidian’s research is focused on developing rules based on data that input all information available on a patient and output the best treatment for that patient. If “x” is all of the information available, C1 equals “0,” and C2 equals “1,” she uses statistics to determine rules “d.” For example, the rule above would have the form:

d(x) = 0(C1) if age <50 and PR level <10

d(x) = 1(C2) otherwise

“You can think of an infinitude of possible rules,” Davidian continued, “but the goal is to find the rule leading to the best outcome. We are developing statistical methods to do this.”

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Science talks on EDCs and smoking update Council

By Ernie Hood

Science marches on, and one way for members of the National Advisory Environmental Health Sciences Council to keep up with new developments in NIEHS research is hearing the two scientific talks typically scheduled into their meetings. At the May 14-15 session, members heard presentations on a new international report on the state of the science for endocrine disrupting chemicals (EDCs), and new intramural findings on genome-wide interactions with smoking.

SOS on EDCs

[Thomas Zoeller, Ph.D.](#), professor of biology at the University of Massachusetts Amherst, briefed Council on the report “[State of the Science of Endocrine Disrupting Chemicals – 2012](#),” issued in February by the United Nations Environment Programme (UNEP) and the World Health Organization (WHO). Zoeller was a co-author and co-editor of the landmark



During his summary of the UNEP-WHO report on EDCs, Zoeller noted that NIEHS has been a major contributor to substantial research progress in the field over the past decade. (Photo courtesy of Steve McCaw)

publication, which updated the 2002 UNEP-WHO “Global Assessment of the State of the Science of Endocrine Disruptors” report, incorporating the considerable progress in the field over the last decade. NIEHS Program Administrator Jerry Heindel was also a co-author and co-editor.

Zoeller said the time was ripe to consolidate recent developments in the field. “There have been major initiatives, both in the U.S. and in Europe and Japan, focused on endocrine disruption, and it was a good time to take stock in where we were, to characterize the information, and think about where it should go and what we’ve learned, to identify key concerns and future needs, and to recognize that chronic, noncommunicable disease is at the highest level in history,” he noted.

The report is comprised of sections focusing on the definition of endocrine disruption, establishing the evidence for endocrine disruption in humans and wildlife, human and wildlife exposures to EDCs, and future needs and emerging issues of concern. “The document represents a single place that has captured a very large amount of information in a way that allows you to see the big picture,” said Zoeller. “When you see, in a single place, the trends that are occurring in reproduction, neurodevelopment, and immunology, etc., I think it makes a much stronger statement.”

Among the significant conclusions included in the report was the concept that experimental studies are demonstrating very clearly the complexity of EDC actions on development and adult physiology, as new science emerges on delayed and epigenetic effects of EDC exposures.

In an April 2013 [EHP editorial](#), NIEHS and NTP Director Linda Birnbaum, Ph.D., described the report as “mandatory reading for everyone who is interested in protecting and improving human health.”

Smoking guns in the genome

In the second Council science talk, “Genome-Wide Interactions With Smoking – Served Two Ways,” intramural researcher [Stephanie London, M.D., Dr.P.H.](#), described two recent research initiatives emerging from her laboratory, using genome-wide analysis techniques to assess the impact of smoking.

The first project incorporated smoking into genome-wide interaction studies of pulmonary function in adults. London’s group, along with collaborators, identified [16 novel loci](#) (specific locations on genes) that are responsible for determining proper lung function. It was a unique approach to genome-wide association studies



London told Council members that in utero exposure to maternal smoking has a dose-response effect on DNA methylation patterns in newborn offspring. (Photo courtesy of Steve McCaw)



London acknowledged the support of her research group as she concluded her presentation. (Photo courtesy of Steve McCaw)

(GWAS), expanding the method to yield previously unattainable results. “This work showed that including environmental factors in GWAS, using joint tests of main effects and interactions, can discover novel loci that you would miss if you analyzed just the genetic main effects alone, and this is true even when the interactions are not strong,” said London.

The second project related findings from studies of [epigenetic interactions with smoking](#), involving maternal smoking during pregnancy and genome-wide DNA methylation in newborns. London’s group, and collaborators from Duke University, the University of North Carolina at Chapel Hill, and Norway, found epigenetic effects suggesting that differing DNA methylation patterns in newborn children of smokers versus non-smokers may play a mechanistic role in adverse health outcomes later in the children’s development.

The work pointed toward two genes known to be associated with response to exposure to polycyclic aromatic hydrocarbons contained in cigarette smoke, and to several other novel genes for smoking effects. “These results support the hypothesis that epigenetic mechanisms may contribute to offspring health effects from maternal smoking in pregnancy, and we also note that the methylation differences seen for adult smoking in other studies are already present at birth in relation to *in utero* exposure,” London explained.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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ONES program celebrates seventh year of excellence

By Eddy Ball

For the scientists who oversee grants at NIEHS, things don’t get much better than the meeting of the Outstanding New Environmental Scientist (ONES) awardees each year and the excitement of learning about new developments in their work. At this year’s annual meeting May 20-21, there was even more reason than usual to cheer, as the program looked forward to its renewal after a yearlong hiatus.

The early career scientists are a select group of high achievers involved in cutting-edge research, funded across the spectrum of science supported by the NIEHS Division of Extramural Research and Training (DERT). In many ways, they represent the best examples of the transdisciplinary collaborative



Council member Vivian Cheung, M.D., of the University of Pennsylvania asked London whether paternal smoking may contribute to the DNA methylation mechanism in newborns. London replied that the researchers had not found an effect for passive smoking exposure in this case. (Photo courtesy of Steve McCaw)



Birnbaum was clearly at home with the group she affectionately described as the “ONESies,” when she told the audience, “This is one of my favorite events of the year. ... You are really exceptional.” (Photo courtesy of Steve McCaw)

spirit that NIEHS tries to foster through its grants and strategic plan, and they embody the promise of the newest generation of environmental health science biomedical researchers.

“The ONES program not only provided the funding to establish your laboratories and careers, but also has a goal to build long-standing relationships with us here at NIEHS,” NIEHS and NTP Director Linda Birnbaum, Ph.D., told the awardees in her opening remarks. “This is very important to us, not just for the goodwill that it builds, but for the continued vibrancy of environmental health research capacity.”

The enormous advantages of being a part of the ONES program were acknowledged by the 27 awardees who made presentations at the meeting, as one after another, they credited NIEHS support for their accomplishments.

“Without this award, much of the work I’m going to present would be impossible,” said Jason Bielas, Ph.D., echoing sentiments expressed by his fellow awardees.

An impressive showcase of young talent

The program was organized around the six NIEHS program administrators who oversee research grants that support ONES awardees. The DERT scientists taking their turns at the podium included Kimberly McAllister, Ph.D., DNA repair and carcinogenesis; Cindy Lawler, Ph.D., neurotoxicology; Jerrold Heindel, Ph.D., early-life exposures; Claudia Thompson, Ph.D., mechanisms of toxicity; Sri Nadadur, Ph.D., indoor and outdoor air exposures, and nanotoxicology; and Les Reinlib, Ph.D., arsenic exposures.

The ONES program has made a total of 42 awards since 2006. Awardees from recent-year groups were joined by five early-career awardees with grants made in 2012. The reconstituted ONES program at NIEHS looks forward to a new batch of awardees in fiscal year 2014.

The presentations drew an audience of scientists from across NIEHS, to listen to and interact with awardees. Several trainees were on hand, many responding to an invitation by NIEHS Deputy Scientific Director Bill Schrader, Ph.D., to learn more about the kinds of research the Institute supports through DERT, and the directions which NIEHS funding is likely to proceed in the future.



Leading the list of presenters was Scott McCulloch, Ph.D., of North Carolina State University. A former trainee in the NIEHS DNA Replication Fidelity Group headed by Thomas Kunkel, Ph.D., McCulloch has used his ONES support to advance his research into “The Role of Human DNA Polymerase eta in the Response of Oxidative Stress.” (Photo courtesy of Steve McCaw)



In Shreffler’s absence, DERT grant administrators rotated as facilitators. McAllister, right, joined ONES awardee Yu-Ying He, Ph.D., photobiologist and former NIEHS trainee, of the University of Chicago, following her presentation on “Role of Autophagy in Response to UV [Radiation] Damage.” (Photo courtesy of Steve McCaw)



Several of the NIH early-career awardees, including Joyce Ohm, Ph.D., of the University of North Dakota, joked about crashing the ONES celebration. Those in the newest group of talented young scientists were welcomed as ONES, because they are, in all but name, part of the chosen ones. (Photo courtesy of Steve McCaw)

An honor role of accomplishments

The ONES coordinator, NIEHS Program Administrator Carol Shreffler, Ph.D., who also oversees training program grants, was unable to attend the meeting for the first time since ONES began in 2006. However, Birnbaum's remarks included some of the impressive metrics Shreffler had amassed for the introduction to a two-volume special issue of the [Journal of Biochemical and Molecular Toxicology](#), published this past January and February.

The special issue featured research publications and mini-reviews from nearly 20 of the ONES awardees, and was co-edited by 2008 ONES awardee Angela Slitt, Ph.D. In Shreffler's [introduction](#), she offered some impressive statistics about the ONES program, in the areas of outstanding publications and productive collaborations; tenure and promotion; service on high-profile journal editorial awards; recognition by home universities, international professional societies, and even the U.S. President; and successful applications for grant funding beyond their ONES awards.

Shreffler's catalogue of honors clearly demonstrated that, in every respect, awardees have exceeded expectations of this unapologetically ambitious program.

As the years go by — ONES awardees 2006-2012

The format has evolved since 2006, but the qualities that remain constant are the enthusiasm of the young scientists, the genuine pride of program administrators, and the *esprit de corps* that fosters fruitful collaborations across the extended family of NIEHS intramural and extramural researchers.

- 2006 — [NIEHS Celebrates ONES Award Winners](#)
- 2007 — [New ONES Grantees to Visit Institute in January](#)
- 2008 — [2008 ONES Awardees Speak at NIEHS](#)
- 2009 — [2009 ONES Awardees Speak at NIEHS](#)
- 2010 — [NIEHS selects 2010 ONES awardees](#)
- 2011 — [NIEHS celebrates five years of ONES research](#)
- 2012 — [Young EH researchers shine at ONES symposium](#)



Lead researchers Steve Kleeberger, Ph.D., left, and Serena Dudek, Ph.D., were among many members of the NIEHS intramural community who turned out for the presentations. (Photo courtesy of Steve McCaw)



Epidemiologist Patrick Ryan, Ph.D., draws upon his NIH early-career award to support his leadership of a cross-disciplinary study of "Neurobehavioral and Neuroimaging Effects of Traffic Exposure in Children," with colleagues at the Cincinnati Children's Hospital Medical Center. (Photo courtesy of Steve McCaw)



The DERT community, including DERT Deputy Director Pat Mastin, Ph.D., turned out in force to support the ONES awards and their grant administrators. Mastin worked closely with Shreffler to get the program off the ground in 2005. (Photo courtesy of Steve McCaw)



ONES research ranges widely, from basic research into DNA repair to human studies, such as the one led by Christy Porucznik, Ph.D., of the University of Utah, on the effects on offspring of parents' periconceptional exposure to such environmental chemicals as bisphenol A. (Photo courtesy of Steve McCaw)

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Barium distributions in teeth reveal early-life dietary transitions

By Sara Mishamandani

A new [study](#) published May 22 in the journal Nature shows that chemical signatures in teeth can be used to uncover aspects of early-life dietary transitions. [Manish Arora, Ph.D.](#), an NIEHS R00 early investigator grantee and former postdoctoral trainee in the Harvard University Superfund Research Program (SRP), led research to develop a method for measuring early-life dietary transitions based on barium variations in teeth.

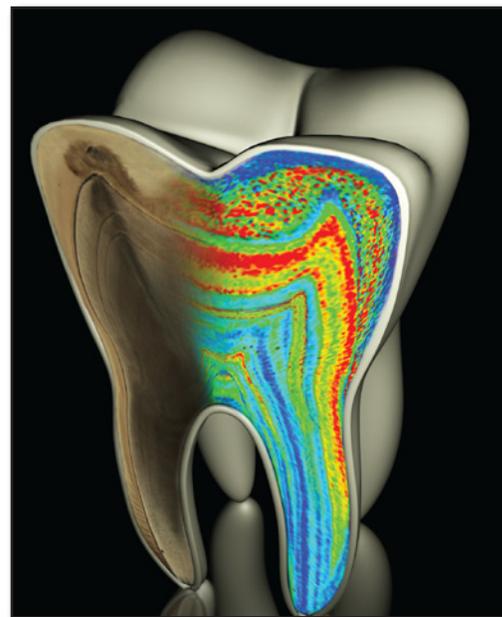


[Listen to NPR Morning Edition story about Arora's study \(03:42\)](#)

[Read Transcript](#)

“Early-life diet, including breastfeeding, is important in so many ways. It is crucial for infant health, but can also serve as a pathway for chemical exposure,” said Arora. “Given that maternal recall of breastfeeding practice and early-life diet can be biased, when recorded many years later, an objective retrospective biomarker would provide a major advance to studies on children’s health.”

Prenatal barium transfer is restricted by the placenta, but marked enrichment occurs immediately after birth from mother’s milk or infant formulas, which contain higher barium levels than umbilical cord sera.



Molar tooth model with the cut face showing color-coded elemental patterns merging with a microscopic map of growth lines, which have been accentuated to reflect their ring-like nature. (Photo courtesy of Ian Harrowell, Christine Austin, and Manish Arora)

In response to these variations in dietary barium exposure, levels in enamel and dentine increase at birth and remain elevated for the duration of exclusive breastfeeding.

Barium levels in teeth rise further with introduction of infant formula, because most cow milk and soy-based formulas contain much higher levels of barium than human milk. Arora's team mapped these barium variations in teeth, using a laser ablation method that he has previously used successfully in studies on lead and manganese exposure.

Wider implications of new insight into evolutionary biology

“There is tremendous need to develop validated biomarkers of past exposures, particularly for use in epidemiologic studies,” said NIEHS Division of Extramural Research and Training Director Gwen Collman, Ph.D. “Dr. Arora's work is exciting, because he shows us new ways to use teeth, a forgotten biospecimen, to measure past exposures. We encourage the application of this technology to other environmental exposures to link early-life exposures to later disease endpoints.”

This method has far reaching applications, according to Arora. It can be applied to epidemiologic investigations of the health consequences of breastfeeding and chemical exposures during early-life, as well as studies on primate evolution. It can also be used to specifically investigate the health effects of barium, and differences between breastfeeding and infant formulas.

“One of the studies we plan to undertake from this work is to investigate how exposure to barium and other elements in early life will affect children's health,” said Arora. “Our biomarker provides a unique opportunity to study breastfeeding and infant formula use, from the perspective of exposure to these elements.”

Arora's team first analyzed teeth from macaques with known diet histories, to refine the method. They later tested teeth of children enrolled in the University of California, Berkeley's Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, where breastfeeding and infant formula use were recorded prospectively. Researchers found that they were able to predict early-life dietary changes in the children, based on this newly developed method.

An interesting application of this method arose when a several thousand-year-old Neanderthal tooth was made available to the team. Using their method, the researchers documented the first early-life dietary transition in a juvenile Neanderthal.

Citation: [Austin C, Smith TM, Bradman A, Hinde K, Joannes-Boyau R, Bishop D, Hare DJ, Doble P, Eskenazi B Arora M. 2013. Barium distributions in teeth reveal early-life dietary transitions in primates. Nature; doi:10.1038/nature12169 \[Online 22 May 2013\].](#)

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

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Manish Arora, right, joined his postdoctoral trainee Christine Austin, Ph.D., in his lab. Austin is first author on the paper. (Photo courtesy of Manish Arora)

NIEHS scientists identify a novel signal for mismatch repair

By Heather Franco

Errors are incorporated into DNA as it is copied by DNA polymerase enzymes, in a process known as DNA replication. Correcting these errors is imperative to prevent detrimental mutations, which can lead to diseases, such as cancer. However, to maintain the genomic stability essential to human health, the repair machinery needs to be directed to the newly copied strand, so as to not introduce mutations into the template DNA.

In a new [study](#) published May 9 in *Molecular Cell*, [Scott Lujan, Ph.D.](#), and colleagues in the NIEHS DNA Replication Fidelity Group, headed by lead researcher [Thomas Kunkel, Ph.D.](#), uncovered an identification signal on the newly copied DNA strand that marks it for repair. They demonstrated, for the first time, the role of a key enzyme, RNase H2, in directing the mismatch repair machinery to the correct strand. This work may lead to a new understanding of the development of some cancers and neurodevelopmental disorders.



First author Lujan is a postdoctoral fellow in Kunkel's group. (Photo courtesy of Scott Lujan)

Understanding mechanisms of mismatch repair

Lujan explained that maintaining genomic integrity is essential for the survival of an organism, and it is achieved through DNA replication and its accompanying repair processes. Each strand of the double helical template DNA is copied in a unique manner, with the leading strand synthesized processively and the lagging strand synthesized in small segments known as Okazaki fragments.

According to Lujan, several specialized enzymes, called polymerases, have evolved to copy the different strands. Interestingly, the leading strand polymerase has a highly conserved sequence that, when introduced into lagging strand polymerases, makes them more prone to insert both ribonucleotides and incorrect DNA bases. The reverse is true when the equivalent sequence from lagging strand polymerases is introduced into the leading strand polymerase.

“It appears that the leading strand polymerase has evolved to prevent more frequent misinsertion of DNA bases, due to this sequence, while maintaining an elevated ribonucleotide insertion rate,” Lujan said. “This implies that leading strand ribonucleotides serve some positive function that outweighs their risk, as their presence leads to genomic instability.”

Study marks a first in mismatch repair research

This study presents the first *in vivo* evidence for a signal that specifically marks the leading strand in eukaryotes. As Kunkel remarked, “Scott’s study and a parallel study published at the same time by Josef Jiricny, of the University of Zurich, and colleagues, give us a better understanding of how this machinery knows which partner in a mismatch is the mistake that needs to be removed. This is important, because the consequences of making the wrong choice are mutations that can have a variety of adverse health consequences.”

Citation: Ghodgaonkar MM, Lazzaro F, Olivera-Pimentel M, Artola-Borán M, Cejka P, Reijns MA, Jackson AP, Plevani P, Muzi-Falconi M, Jiricny J. 2013. Ribonucleotides misincorporated into DNA act as strand-discrimination signals in eukaryotic mismatch repair. *Mol Cell* 50(3): 323-332.

One mechanism by which errors in the DNA sequence are corrected is mismatch repair, in the study of which Kunkel has been a leading authority for almost 20 years. As Kunkel explained, “Mismatch repair of replication errors is like the spell-check function on a word processor, and is critical for correctly duplicating genetic information.” As part of the repair process, he said, the ribonucleotides are excised and repaired by the ribonucleotide excision repair machinery, including RNase H2. Kunkel, Lujan, and the rest of the team hypothesized that the incorporation and repair of the ribonucleotides pinpoints the newly copied leading strand for repair.

Using the budding yeast *Saccharomyces cerevisiae*, Lujan demonstrated that, in the absence of RNase H2, the rate of mismatch repair is reduced specifically on the leading strand. Interestingly, reducing the number of ribonucleotides incorporated into the DNA strand diminished the impact of ribonucleotide excision repair on the proficiency of mismatch repair. As Lujan concluded, “Both the number and repair of ribonucleotides affect the mismatch repair efficiency on the leading strand.”

Linking DNA repair to human disease

There is a high degree of conservation in mismatch repair among eukaryotes. In fact, mutations in the mismatch repair machinery lead to a predisposition for cancer and, specifically, Lynch syndrome, a genetic condition that greatly increases the risk of colon cancer. Further, mutations in RNase H2 cause Aicardi–Goutières syndrome, a congenital immune-mediated neurodevelopmental disorder that is generally fatal within the first few years of life. From these pioneering studies on DNA repair mechanisms, researchers have gained new insights that are potentially relevant to the etiology and treatment of a number of human diseases.

Citation: [Lujan SA](#), [Williams JS](#), [Clausen AR](#), [Clark AB](#), [Kunkel TA](#). 2013. Ribonucleotides are signals for mismatch repair of leading-strand replication errors. *Mol Cell* 50(3):437-443.

(Heather Franco, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Reproductive Developmental Biology Group.)

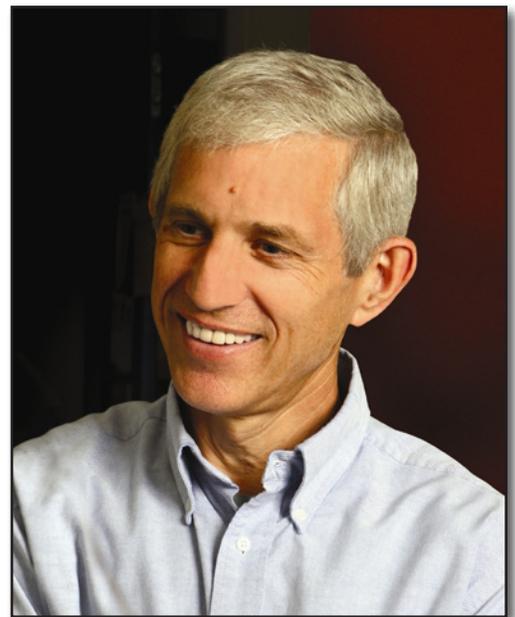
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New plant research discoveries could benefit global agriculture

By *Carol Kelly*

Research, supported in part by NIEHS, is addressing big questions about plant growth, and offers potential solutions for meeting increased agricultural demand, globally.

An international group of scientists, led by [Julian Schroeder, Ph.D.](#), professor of cell and developmental biology and NIEHS Superfund Research Program (SRP) grantee at the University of California, San Diego (UCSD), has discovered important properties about the ways plants grow and upload nutrients, which could beneficially affect global agriculture.



Kunkel holds appointments in the NIEHS Laboratory of Molecular Genetics and Laboratory of Structural Biology, where he formerly served as chief. (Photo courtesy of Steve McCaw)

The [discoveries](#), published May 2 in Nature, centered on transport proteins within plant cell membranes. Transport processes are crucial, enabling plants to survive environmental stresses, including those anticipated to result from global climate change. With improved transporters, plants can better resist toxic metals and pests, increase salt and drought tolerance, control water loss, and expand energy storage.

“Many recent plant discoveries around the world have previously been under the radar — known only to a small group of plant biologists — but, by disseminating these findings widely, we hope to educate policymakers and speed the eventual application of recent discoveries,” said Schroeder.

Addressing food deficiencies

Implications from the new research for increasing the supply of food include enhanced staple crop yields, increased nutrient content, and improved tolerance to unfavorable soil conditions, which could mean farming on previously unusable or marginally useable land. With the global population expected to reach 9 billion by 2050, improving nutritious and sustainable food production is essential for human and environmental health, according to the U.K. Government Office for Science Foresight project Global Food and Farming Futures final [report](#).



One project in Schroeder's interdisciplinary lab focuses on identifying genes that mediate sodium stress and drought resistance, and heavy metal uptake and detoxification in plants. (Photo courtesy of Julian Schroeder)



Linked video:
[Watch interviews with members of the Food and Farming Futures Project on the implications of food security and climate change \(04:56\)](#)

(Launches in new window)

Download Media Player:  Flash 

Schroeder discovered a sodium transporter, named HKT1, which plays a key role in protecting plants from soil salinity stress, a contributor to major crop losses. In field trials using durum wheat, a staple commercial grain crop, agricultural scientists found that a particularly active member of this HKT1 transporter family removed excess sodium from plant leaves. As a result, crop yields were boosted by 25 percent.

“Saline soils are causing increasing losses in agriculture yields globally,” said Schroeder. “More fundamental knowledge and basic discovery research is needed, and would enable us to fully exploit these advances and pursue new promising avenues of plant improvement, in light of food and energy demands and the need for sustainable yield gains.”

Plants are the major point of entry for essential nutrients into the food chain, and the work of collaborator [Mary Lou Guerinot, Ph.D.](#), a molecular geneticist, contributes to understanding how plants absorb and distribute essential metals, such as iron, and toxins, such as arsenic ([see story](#)). In conjunction with SRP research at



Along with analyzing plant iron content to search for mutants that can more readily absorb iron, Guerinot researches harmful metal uptake in edible plants, such as arsenic and cadmium in rice. (Photo courtesy of Dartmouth College)

Dartmouth College, Guerinot's work is laying the foundation for crops, particularly rice, that have higher micronutrient levels and offer safer, sustainable solutions for malnutrition.

More than two billion people worldwide are malnourished and have diets with deficiencies in essential nutritional minerals, such as iron and zinc, according to the paper's authors.

Investigating toxicant accumulation in plants

The UCSD SRP is also working to determine the molecular mechanisms by which plants accumulate toxicants. They are investigating the potential for phytoremediation, a process in which green plants are intentionally chosen for planting in certain areas, based on their ability to uptake harmful chemicals from contaminated land. Schroeder's lab collected and is analyzing plant samples from a brownfield site owned by the Jacobs Center for Neighborhood Innovation in southeastern San Diego. A brownfield site is land for which redevelopment or reuse may be complicated by the presence, or potential presence, of a hazardous substance, pollutant, or contaminant.

"This research will help us avoid accumulation that harms crop plants, but also enhance bioremediation through noncrop plants that do accumulate toxicants," said Schroeder.

Citation: Schroeder JI, Delhaize E, Frommer WB, Guerinot ML, Harrison MJ, Herrera-Estrella L, Horie T, Kochian LV, Munns R, Nishizawa NK, Tsay YF, Sanders D. 2013. Using membrane transporters to improve crops for sustainable food production. *Nature* 497(7447):60-66.

(Carol Kelly is a health communication specialist with MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)



The Jacobs brownfield site, shown above, is in a community where exposure to toxicants in land and water is a concern. Investigators in the UCSD SRP hope to identify plants that could help clean up the contaminated land. (Photo courtesy of UCSD)

Researchers at NIEHS discover role for a unique complex in DNA repair

By Heather Franco

Mutations in genes encoding proteins in the MRN complex and Ctp1 have been implicated in the origin of human diseases, characterized by markedly greater sensitivity to DNA damage and increased susceptibility to cancer. These proteins are involved in homology-driven recombinational repair (HDRR), a mechanism of DNA double-strand break (DSB) repair.

In a [study](#) published March 28 in PLOS Genetics, NIEHS [Chromosome Stability Group](#) biologist James Westmoreland and lead researcher Michael Resnick, Ph.D., provide the first direct evidence that the yeast homologs of these proteins — the MRX complex and Sae2 — coordinate the initiation of HDRR at both ends of the DSB. Since exposure to environmental agents can cause DSBs, these results highlight the importance of this complex in yeast and humans.

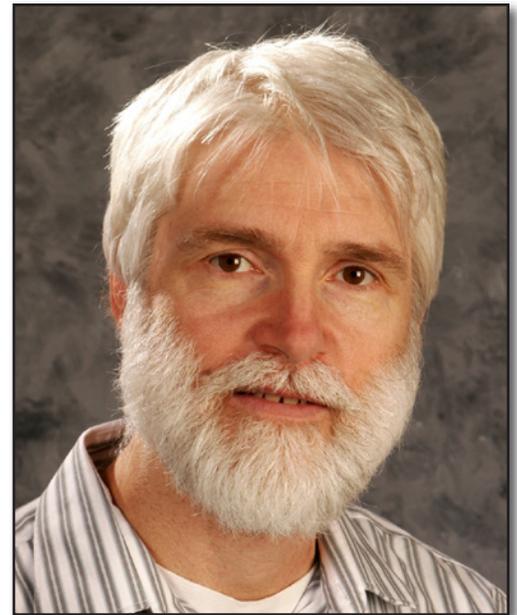
The ability to investigate coincident resection during HDRR was aided by two factors — the development of a new technology and the use of yeast as a model system. Prior to this study, it was not possible to directly distinguish resection at one versus two ends of a DSB. Therefore, Westmoreland developed a new technology called two-dimensional pulsed-field gel electrophoresis (2D-PFGE) to observe this phenomenon ([see text box](#)).

Resnick described why they used yeast, rather than another organism, for these experiments. “Yeast has often served as a test tube for human function. There is strong conservation in many basic cellular processes, including DSB repair, from yeast to humans.” He added that yeast can also maintain circular chromosomes, which provide unique advantages to the study of DSBs and coincident resection.

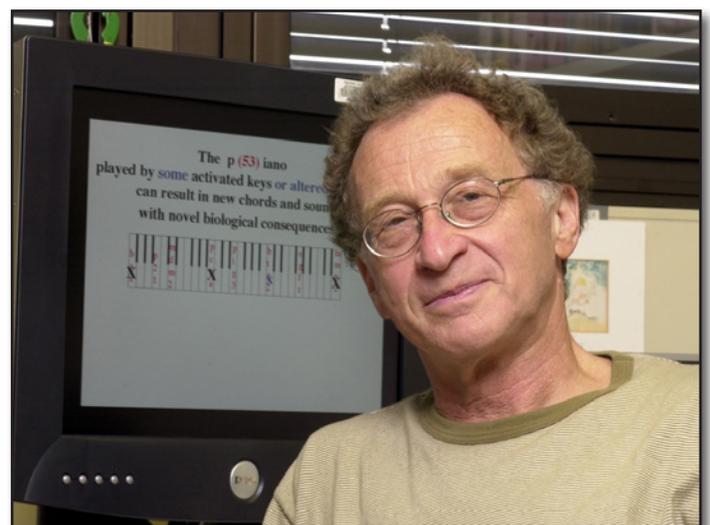
Resolving DSBs in DNA

Westmoreland said DSBs can be caused by many environmental agents and can lead to genomic instability, including gross chromosomal rearrangements and carcinogenic mutations, if left unrepaired. Two mechanisms have evolved to resolve DSBs — nonhomologous end-joining and HDRR. “HDRR is unique because it provides for accurate repair of broken or gapped regions of the DNA,” Westmoreland said.

In HDRR, DNA base pairs at the ends of the break need to be cut away to generate a single stranded DNA, in a process known as resection. The single-stranded DNA can then insert itself into the homologous region of its sister chromosome and act as a template for repair.



First author Westmoreland (Photo courtesy of Steve McCaw)



Resnick is head of the Chromosome Stability Group in the NIEHS Laboratory of Molecular Genetics. (Photo courtesy of Steve McCaw)

Resection occurs in two stages. First, a few base pairs are removed, making a small single strand gap in the DNA. Second, resection is greatly extended so that kilobases of base pairs are excised, exposing a large region of single-stranded DNA. Until now, it hasn't been clear if resection occurs at one or both ends of the break. Resection at only one end of the break is postulated to increase the instability of the DNA. Therefore, resection at both ends of the break, known as coincident resection, appears to be the favored mechanism.

Extrapolating results from the yeast model to humans

Through analysis of mutant yeast strains, Westmoreland and Resnick demonstrated that the MRX complex and Sae2 are essential for the initiation of coincident resection with differing degrees of necessity, depending on the type of break and a more stringent requirement in repair of "dirty" breaks. A dirty break occurs when there is additional damage to the region of the DSB end that prevents a simple rejoining or ligation of the ends. The finding of additional requirements for repair is important, since DSBs induced by environmental agents are often likely to have dirty ends.

The results of this study have broad implications for human health. In fact, a mutation in the NBS1 gene, which is a component of the MRN complex, causes Nijmegen breakage syndrome, an inherited disease in which the body's DNA is prone to breakages resulting in a number of issues, including frequent infections and an increased risk of developing cancer.

By understanding the mechanism of coincident resection during DSB repair in yeast, as well as describing new roles for the MRX, complex and Sae2, researchers have gained insight into the etiology of, and potential therapeutic targets for, human diseases.

New technology allows for novel discovery

In pulsed-field gel electrophoresis (PFGE), electrical currents change direction along the length of an agarose gel in a zigzag pattern, which allows for the separation of larger DNA molecules than is possible with a standard agarose gel. Through rigorous analysis, the researchers were able to identify DNA molecules that had undergone resection at 0, 1, or 2 ends — m , m^* , and m^{**} , respectively — based on their migration pattern. They discovered that molecules resected at both ends migrated less than those that had not undergone resection or undergone one end resection. The migration in the gel was opposite to initial expectation, in that with the reduction in mass due to resection, there was decreased migration. While the reason why this reduction occurs remains a mystery, it is somehow tied in with the conformation of single strand DNA under PFGE conditions, which on its own would be an interesting topic for future study, according to the researchers.

Westmoreland then further analyzed the molecules with presumed one-end (m^*) and two-end (m^{**}) resections identified in the round of PFGE by subsequently applying PFGE in a second dimension. From this second analysis, he was able to demonstrate that the intermediate resections were actually resections at only one end and not a reduced length of excision at each end of DSBs. As a result, with his development of 2D-PFGE, Westmoreland could observe, for the first time, resection at 0, 1, or 2 ends of a DSB.

Citation: [Westmoreland JW, Resnick MA. 2013. Coincident resection at both ends of random, gamma-induced double-strand breaks requires MRX \(MRN\), Sae2 \(Ctp1\) and Mre11-nuclease. PLoS Genet 9\(3\):e1003420.](#)

(Heather Franco, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Reproductive Developmental Biology Group.)

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Superfund program director discusses mining waste solutions in Armenia

By Sara Mishamandani

With its years of lessons learned from basic research and applications in the field, NIEHS-funded Superfund Research Program (SRP) remediation of toxic waste sites has emerged as a model for countries around the world.

Understanding how to keep metals from spreading to communities adjacent to toxic waste sites, and reversing the damage in nearby land, are what inspire [Raina Maier, Ph.D.](#), director of the University of Arizona (UA) SRP, and an expert in environmental microbiology. As part of SRP commitment to outreach, Maier is eager to share findings from research at former mining sites in the southwestern U.S. and northern Mexico with scientists facing similar situations in their own countries.

During the International Scientific Symposium on Emerging Issues in Environmental and Occupational Health: Mining and Construction in Transition Economies April 22-23 in Yerevan, Armenia, Maier presented her research on [Phytostabilization of Mine Tailings: Metal Speciation and Dust Suppression](#), a process by which plants remove, detoxify, or stabilize toxic substances.

The [international symposium](#), sponsored by the American University of Armenia, Collegium Ramazzini, NIEHS, and others, was designed to raise awareness of health issues related to the mining industry in Armenia. The meeting brought together occupational and environmental health scientists, to advance understanding of how to protect worker and community health in the region.

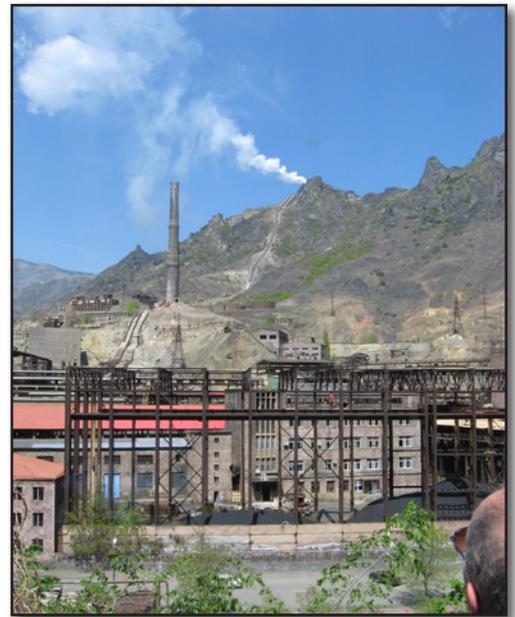
Mining is important to the Armenian economy, but there is increasing recognition of the negative effects of mining on human and environmental health, and awareness that existing environmental regulations are not currently well enforced.

Applying Superfund research to Armenia

After describing the purpose and goals of the SRP to her audience, Maier presented her research on phytoremediation of mining wastes, also called mine tailings. Mine waste often contains toxic metals, which people can inhale through dust. In Arizona, Maier and her colleagues have identified suitable native plants and conditions that allow them to grow where mine contamination is found. The plants stabilize the tailings, keeping them from spreading long distances through wind erosion. These plants also help detoxify the land, by stabilizing toxic metals in the root zone.



Maier and her group have translated research on biological factors and processes influencing the transport and fate of bacteria and contaminants in the environment into the development of potential biomedical and environmental applications. (Photo courtesy of UA)



The smelter smokestack in operation in Akhtala, Armenia, spreads lead and other metals onto surrounding land. (Photo courtesy of Raina Maier)

Maier also discussed informational materials developed by UA that are used to educate and inform affected communities near mining sites. She gave examples with UA SRP informational fact sheets for community members, such as [What Are Mine Tailings?](#), [What Is Arsenic?](#), and [Lead and Our Health](#).

After Maier's talk, a faculty member from the American University of Armenia expressed interest in initiating phytoremediation field trials at mining sites in Armenia. A future collaboration on this project is now in the planning stages. University students said that they would like to translate existing UA SRP informational materials into Armenian, for use in local communities.

"Armenia is a beautiful country and faces the same environmental challenges associated with mining that are found in other places of the world," said Maier. "I look forward to working with the American University of Armenia to begin to address those challenges."

Health implications in the community

Maier participated in a field trip to Akhtala, Armenia to see a smelter in operation, and learn about local conditions and environmental concerns related to mining development. An elevated smokestack was installed at the smelter in 2010, in an attempt to reduce the amount of lead in local soil, but it has instead resulted in further spread of lead throughout the valley. Lead exposure creates a serious neurological health risk, especially to children.

"The movement of lead from the smelter emphasizes the need to better understand what mining workers and surrounding communities are being exposed to," said Maier. "It also shows us how important it is to stabilize mining waste and keep it from affecting local communities."

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)



Environmental health science experts from around the world participated in the international scientific symposium. Shown in the front row, seated left to right, are Karyl Norcross Mehlman, M.D., Ph.D., of the Mount Sinai School of Medicine; Morando Soffritti, M.D., of the Ramazzini Institute; and Varduhi Petrosyan, Ph.D., of the American University of Armenia. (Photo courtesy of Raina Maier)

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Congressional briefing highlights organs-on-a-chip

By Paula Whitacre

A translucent device the size of a rubber eraser that contains not just the cells of a human organ, but also carries out that organ's functions — that's the exciting potential of biomimetic microsystems, new technology more descriptively called human “organs-on-a-chip” after its launch with the help of NIEHS.

Donald Ingber, M.D., Ph.D., founding director of the Wyss Institute for Biologically Inspired Engineering at Harvard University, explained this breakthrough technology at a May 15 briefing on Capitol Hill, sponsored by the Congressional Biomedical Research Caucus (CBRC). “The chips change the paradigm,” said Ingber. “We are engineering microchips, containing living cells that can reconstitute organ-level functions, for drug-screening, diagnostic, toxicologic, and therapeutic applications.”



Ingber explained how human “organs-on-a-chip” have the potential to transform many areas of biomedical research at a May 15 briefing on Capitol Hill. NIEHS funding provided critical early support for the concept. (Photo courtesy of Charles Votaw)

NIEHS provided funding to George Whitesides, Ph.D., Ingber, and other researchers that led to the creation of a lung-on-a-chip. It was the first of about a dozen devices now in various stages of development, including gut, kidney, and bone marrow. As Ingber explained, the NIEHS-supported [Nano-Scale Tools for Use in Cell Biology](#) project showed that, while nanoparticles in themselves do not seem to impact lung cells or tissues, the addition of breathing motion increases toxicity and inflammation — something the chip could detect, but could not be seen in standard cell culture studies.

“With this little rubber chip, we were not just mimicking function, but predicting it,” said Ingber. Animal testing confirmed the finding, and the breakthrough was published in a [2010 paper](#) in the journal *Science*.

Leveraging biological principles

At the briefing, Ingber posed a problem that organs-on-a-chip can potentially solve. “More than \$2 million is spent to test a single compound, and testing takes years to complete,” he said. In addition, large numbers of animals are used, and there can be difficulty in extrapolating lab animal results to human. As an alternative, the chips can be used to construct human disease models and test drug effectiveness.

In 2011, the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), and the Defense Advanced Research Projects Agency (DARPA) announced a collaboration to develop cutting-edge technologies, such as these chips, to predict drug safety. “This is an unprecedented opportunity to speed development of effective therapies, while saving time and money,” noted NIH Director Francis Collins, M.D., Ph.D., when President Obama announced the collaboration.

Ingber's lab received funding from DARPA, to develop automated instruments that will be able to construct the devices that postdocs now, painstakingly, put together. “We are just at the beginning, and it's not sophisticated,” he said. “But the feasibility is there, and we're excited.”

In addition, NIH and FDA are supporting development of the Heart-Lung Micromachine, to connect the lung-on-a-chip with a heart device developed in the lab of Kevin Kit Parker, Ph.D., also at the Wyss Institute. “Our long-term vision is a virtual human body on a chip,” said Ingber.

As Ingber explained, the Wyss Institute was established in 2009 to leverage biological principles for developing new engineering innovations. Collaboration among pharmaceutical companies, government agencies, and academia is a hallmark, and, he said, measures of success include not only publications — at least one paper per month in the journals *Science* or *Nature*, for the last 52 months, with 14 core faculty — but also patents, startups, and other economic results.

Supporting biomedical research on the hill

The CBRC, a bipartisan group that broadens support and knowledge of basic and clinical biomedical research issues throughout Congress, sponsored Ingber’s presentation, which was well attended by congressional staff members. The Coalition for Life Sciences, which serves as scientific advisor to the caucus, organized the event.

(Paula Whitacre is a contract writer with the NIEHS office in Bethesda, Md.)

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Smartphone technology makes exposure assessment more personal

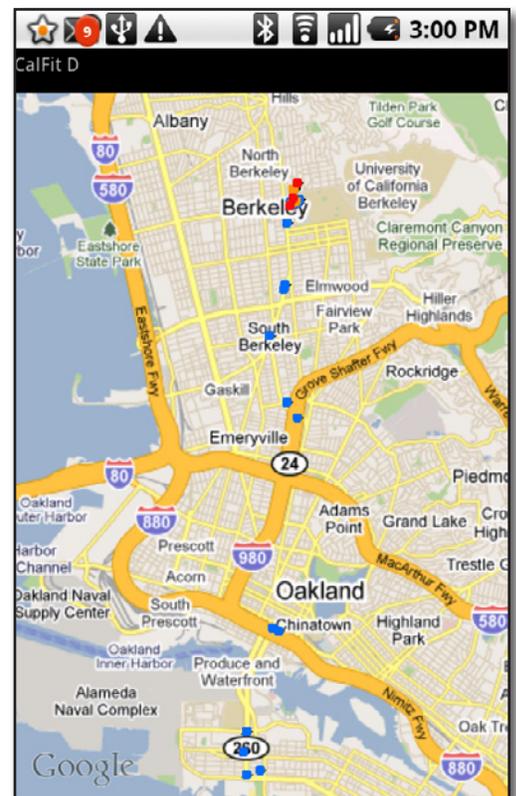
By Nancy Lamontagne

In a new study, partially funded by NIEHS, the CalFit smartphone application developed at the University of California (UC), Berkeley improved air pollution exposure assessment, by providing personal data on time-location patterns and physical activity. Smartphone applications offer an inexpensive and easy-to-use way to gather personal exposure data.

“Having personalized information about where and when people are exposed to pollution raises questions about trade-offs that we haven’t been able to think about before,” said NIEHS grantee [Michael Jerrett, Ph.D.](#), of the UC Berkeley School of Public Health. “For example, if we encourage people to use public transit or to increase their physical activity by walking or biking, are we increasing their exposure to air pollution?”

Research-grade data

Developed by [Edmund Seto, Ph.D.](#), at UC Berkeley, who jointly serves as lead researcher on the study with Jerrett, CalFit runs on Android smartphones, using the phone’s accelerometer to collect data on the user’s energy expenditure associated with physical activity, and its global positioning system (GPS) to pinpoint geographic location. The researchers previously demonstrated that CalFit provides research-grade information that matches the accuracy of gold standard GPS and accelerometry instruments.



This CalFit screenshot shows the GPS capability for tracing where a person spends time during the day. (Photo courtesy of Edmund Seto)

In the new [study](#), 36 people in Barcelona, Spain used CalFit to track their activity and location, and then the researchers linked the phone data with pollution maps. One key finding was that, on average, travel accounted for only six percent of the study participants' time, but this short time period accounted for 24 percent of their daily-inhaled nitrogen dioxide (NO₂). NO₂ is found in vehicle emissions and can cause respiratory problems, especially for people with asthma.

Although scientists know that pollution is higher during times when most people commute, typical air pollution assessment methods don't provide data on when, and for how long, a person is in an area with high levels of air pollution. Most studies use fixed-site pollution monitoring stations, or home addresses and pollution dispersion models to estimate exposure. Tracking physical activity is also key for determining a person's actual inhalation of air pollution, since a person can inhale up to seven times more air pollution on a bike than when in a car, for example.

Adding more personal information

In an NIEHS-funded follow-up study, the researchers are adding ecological momentary assessment to the CalFit information, to gain additional mood and behavior information from users. Five to seven times a day, a survey screen appears on the user's phone. The survey includes a wide range of questions aimed at gathering information, such as whether the user is aware of exposures, why the person was exercising at that time, and how the user felt while exposed to air pollution.

In other NIEHS-funded work, the researchers are collaborating with a research team at the University of Cambridge to develop a portable pollution monitor that will run alongside the CalFit software. Jerrett said that the UC Berkeley team is also designing its own air pollution sensors, to maximize battery life, be portable, and link directly with CalFit.

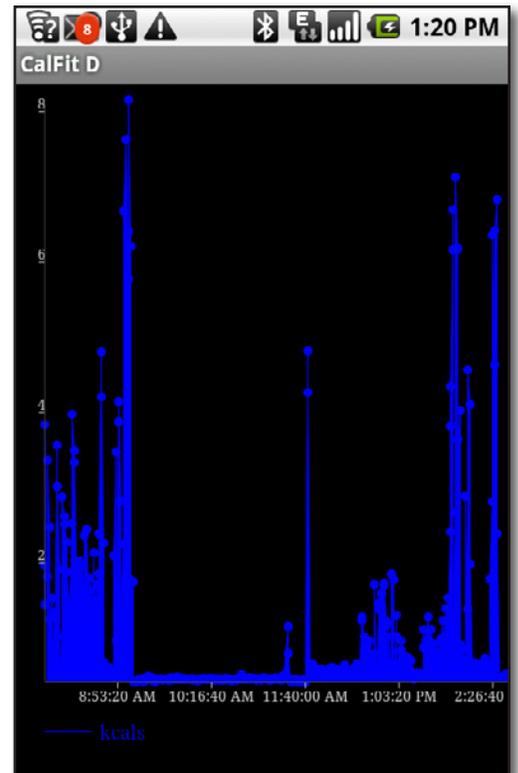
A long-term goal for scientists, developing cell phone-based exposure monitoring technology, is to one day have a large group of volunteers whose exposure-related data is gathered via their cell phones, sent to a server in real time, and then displayed on the Internet without personally identifiable information.

"This information could be used to better understand aspects of population exposure, such as how many people are active when pollution levels are high," Jerrett said. "It could also be used to alert sensitive groups, such as people with asthma, that pollution levels are currently high in a certain area."

Citation: de Nazelle A, Seto E, Donaire-Gonzalez D, Mendez M, Matamala J, Nieuwenhuijsen MJ, Jerrett M. 2013. Improving estimates of air pollution exposure through ubiquitous sensing technologies. *Environ Pollut* 176:92-99.

(Nancy Lamontagne is a science writer with MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

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The application can also track the relative levels of energy expenditure for a person during the day. (Photo courtesy of Edmund Seto)

Early life socioeconomic factors influence development of rheumatoid arthritis

By Robin Arnette

Growing evidence, including a new study on rheumatoid arthritis (RA) by scientists at NIEHS, shows that exposures in early life can have long-term impacts on health.

Researchers found that children who experience adversity, such as food insecurity, have an increased risk of developing RA as adults. The [article](#) appeared in the March issue of *Annals of the Rheumatic Diseases*, and is the first report to link childhood food insecurity with adult RA. The findings were the result of analysis of data from the NIEHS [Sister Study](#), a nationwide study of more than 50,000 women examining the environmental and familial origins of breast cancer.

Not having enough to eat was one of several characteristics considered as possible markers of lower socioeconomic status (SES), which also included young maternal age, and low household income and education level. The scientists were surprised to find, as a whole, lower SES was just as likely to be associated with RA as cigarette smoking, a well-known RA risk factor.

“Given the strength of this SES effect, we really need to understand what’s driving it,” said Christine Parks, Ph.D., a scientist in the NIEHS Epidemiology Branch and lead author of the work.

Looking for the cause of RA

RA is a systemic autoimmune disease in which a person’s body mistakenly attacks its own cells, leading to widespread and damaging inflammation in the joints. Parks initiated the research, because a small, but growing, body of literature suggests certain early life exposures and stressors could impact the developing immune system, with lifelong effects across many different diseases. The paper also examined other prenatal and birth characteristics, but none seemed to change the observed SES effects on disease risk.

Although the research relied on self-reporting — women saying they had been diagnosed with RA — Parks and her colleagues took steps to validate the participants’ responses.

“We know RA may be confused with rheumatism and other forms of arthritis, so if they answered yes to RA, we confirmed their diagnosis by looking at whether they were taking specific immunosuppressant medications, called disease-modifying anti-rheumatic drugs (DMARDs), or whether they reported specific symptoms and were taking steroids for RA,” Parks explained.

Based on this definition, Parks said less than 1 percent of the cohort had a diagnosis of clinically treated RA, but this number was likely an underestimate, since women receiving substandard care, or who experienced nonclassic symptoms, would have been excluded. The research team also took blood samples at enrollment, so future studies will examine early life exposures in relation to RA auto-antibodies and inflammatory markers, along with other autoimmune diseases, such as systemic lupus erythematosus.



Parks said a few studies have also shown effects of maternal stress on later stress and immune responses in children. If true, the socioeconomic adversity and stressors that mothers endure may cross generations. (Photo courtesy of Steve McCaw)

Link between trauma and disease?

Parks said autoimmune diseases include more than 80 clinically distinct conditions. They affect between 5 and 8 percent of the U.S. population, and are among the top causes of mortality in reproductive-age women. If the biologic effects of early stress and lower SES on immunity are nonspecific, which Parks feels is likely, the study's findings may suggest that childhood SES and related exposures could substantially impact autoimmune disease risk in the population.

While traumatic stressors during childhood are widespread in the population, Parks believes they may be more frequently experienced in women with lower SES, or have a greater impact on children who have fewer economic or social resources to buffer their effects. As part of ongoing efforts to understand the effects of childhood SES on the development of RA, her plans include the future examination of extensive information from cohort participants on their other early life environmental characteristics, social support, and traumatic stressors. She sees this work as part of a larger public health issue, and thinks this research adds to a growing understanding that childhood adversity may contribute to the development of many other chronic illnesses.

Citation: Parks CG, D'Aloisio AA, DeRoo LA, Huiber K, Rider LG, Miller FW, Sandler DP. 2013. Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis in adulthood. Ann Rheum Dis 72(3):350-356.

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Superfund researchers well represented at combustion research meeting

By Sara Mishamandani

Leaders in the field of combustion research, from academia, government, and industry, gathered in New Orleans May 15-18 for the [13th International Congress on Combustion By-Products and Their Health Effects](#). NIEHS and NTP Director Linda Birnbaum, Ph.D., who gave the keynote address at the meeting, was on hand as NIEHS-funded Superfund Research Program (SRP) grantees presented important findings related to the Gulf oil spill, and two SRP researchers received awards of excellence.

Louisiana State University (LSU) SRP Center Director Barry Dellinger, Ph.D., and lead researcher Stephanie Cormier, Ph.D., organized the meeting.

New developments in combustion research

Dellinger co-led a session on emissions, remediation, combustion, and toxicity related to the Deepwater Horizon oil spill. During Dellinger's session, LSU SRP researcher Slawo Lomnicki, Ph.D., [reported](#) that environmentally persistent free radicals (EPFRs) were found in tar balls collected from Gulf of Mexico shores after the oil spill. LSU SRP research focuses on [EPFRs](#), which are newly identified pollutant particles that form in combustion, such as the burning of fossil fuels.



During a break in the meeting, Birnbaum, left, spoke with Brian Gullett, Ph.D., an environmental engineer in the U.S. Environmental Protection Agency Office of Research and Development. (Photo courtesy of Maud Walsh)

Emissions from combustion continue to be a controversial environmental issue. The risks associated with the widespread use of combustibles have increased awareness of dioxins and other organic pollutants, nitrogen oxides, sulfur oxides, complex mixtures, metals, and fine particulate matter. While the main focus of the conference was on the origins, fate, and health effects of combustion emissions, it also included all forms of thermal treatment of hazardous substances at Superfund sites.

SRP scientists awarded for their achievements

During the meeting, University of California (UC), Berkeley SRP project leaders Catherine Koshland, Ph.D., and Donald Lucas, Ph.D., received the Adel Sarofim Award for Excellence in Combustion Research.

Koshland has made noteworthy contributions to understanding the role of air pollution from an environmental health systems perspective. Lucas has significantly advanced understanding of combustion-generated air pollutants through the use of experimental chemical kinetics, novel diagnostic techniques for hazardous species, and combustion chemistry. Together, Koshland and Lucas have published 48 manuscripts as co-authors and mentored approximately 90 graduate students, postdoctoral students, and visiting researchers.

The award was established in 2007 to honor Adel Sarofim, Sc.D., an internationally renowned chemical engineering researcher, for advancing understanding of the mechanisms of pollutant emissions from combustors. The award is given by the executive committee of the international congress for outstanding contributions to the understanding of pollutant formation and emissions from combustion processes, and for extraordinary effort towards mentoring of candidates in the research field of combustion and health effects. Former winners include Dellinger, in 2009, and NIEHS SRP Director Bill Suk, Ph.D., in 2011.

Founded in 1990, the international congress meets biennially. This meeting's six plenary sessions covered health effects of emissions, environmental fate of pollutants from combustion sources, environmental sampling technologies, and mechanisms of toxicology of pollutants from combustion sources. Several SRP investigators and trainees presented during oral sessions and a poster session.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

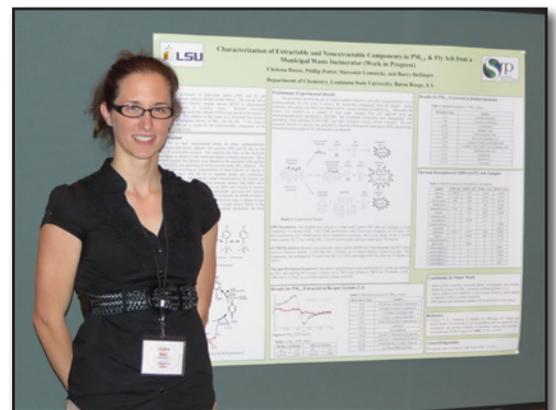
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Adel Sarofim Award winners Koshland, left, and Lucas (Photo courtesy of Maud Walsh)



SRP trainees were an important part of the meeting. Oregon State University SRP trainee Andy Larkin, Ph.D., left, and LSU SRP trainee Lucy Kiruri both gave oral presentations. (Photo courtesy of Maud Walsh)



LSU SRP trainee Cholena Russo presented her research at the poster session on chemical components in fine particulate matter and fly ash from a municipal waste incinerator. (Photo courtesy of Maud Walsh)

Researchers pinpoint gene expression changes associated with human cancers

By Nancy Lamontagne

Supported in part by NIEHS, a team of researchers has analyzed the metabolic gene expression changes associated with cancer and identified hundreds of potential drug targets. Unlike previous studies that focused on a few genes involved in tumor metabolism, the new work analyzed gene expression data from 22 types of human tumors.

The new [study](#) showed that gene expression changes associated with tumor-related metabolism vary significantly across tumor types. Cancer cells must reprogram their metabolism to support the synthesis of new cellular components and generate the energy required for uncontrolled proliferation. For example, tumor cells shift from oxidative respiration to aerobic glycolysis.

The researchers hypothesize that the initiation and accumulation of random mutations in nuclear DNA fuels carcinogenesis and the metabolic changes that occur as cancer progresses. “Environmental mutagens, in particular, likely play a substantial role in the origin and incidence of cancer, by damaging DNA and increasing the rate at which mutations accumulate,” said NIEHS Outstanding New Environmental Scientist (ONES) grantee [Jason Bielas, Ph.D.](#), who was part of the research team. “Given the critical role of DNA mutations in cancer, a mechanistic understanding of the environmental factors that accelerate mutation should aid in the identification of risk factors and methods that prevent and/or slow disease.”

From global metabolism network to individual reactions

To understand metabolic gene expression in different cancers, the researchers, led by [Dennis Vitkup, Ph.D.](#), at Columbia University, used a large collection of gene expression profiles accumulated over the last decade. They compared gene expression in tumors and corresponding normal tissues at several levels of biochemical organization — the global metabolism network, individual biochemical pathways, and individual enzymatic reactions. Bielas, a researcher at the Fred Hutchinson Cancer Research Center and affiliate assistant professor at the University of Washington School of Medicine, designed and supervised experimental research and data analysis for the metabolic profiling.

The researchers did not find any universal changes in tumor-induced gene expression across the human metabolic network, but they did observe that expression changes in some pathways, including upregulation of nucleotide biosynthesis and glycolysis, appear to be more frequent across tumors. Changes tied to the oxidation phosphorylation pathway were present, but less frequent. When looking at individual biochemical reactions, the analysis revealed many hundreds of metabolic enzymes that underwent significant and tumor-specific expression changes and could, thus, be potential targets for cancer therapies.



Bielas received an NIEHS ONES award in 2010, which he uses to study the environmental link between the induction of mitochondrial DNA mutations and cancer, aging, and disease. (Photo courtesy of Jason Bielas)

The researchers found heterogeneous behavior at all levels of biochemical organization, which means that developing cancer therapies that target metabolism will require an understanding of the metabolic changes that occur in each specific cancer type.

Bielas said that the new results support findings from his previously published NIEHS-funded [study](#) which found that, compared to non-tumor tissue, human colorectal tumor tissue mitochondrial DNA exhibited a decreased prevalence of random single base substitutions induced by oxidative damage. This lower frequency in mutations was associated with a shift in glucose metabolism from oxidative phosphorylation to anaerobic glycolysis. These findings suggest that normal mitochondrial DNA mutation rates may prevent cancer progression, and Bielas hypothesizes that cancer therapies designed to increase mitochondrial DNA damage might suppress malignant growth.

Citation: Hu J, Locasale JW, Bielas JH, O’Sullivan J, Sheahan K, Cantley LC, Heiden MG, Vitkup D. 2013. Heterogeneity of tumor-induced gene expression changes in the human metabolic network. *Nat Biotechnol*; doi:10.1038/nbt.2530 [Online 21 April 2013].

(Nancy Lamontagne is a science writer with MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

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This month in EHP

By *AUTHOR*

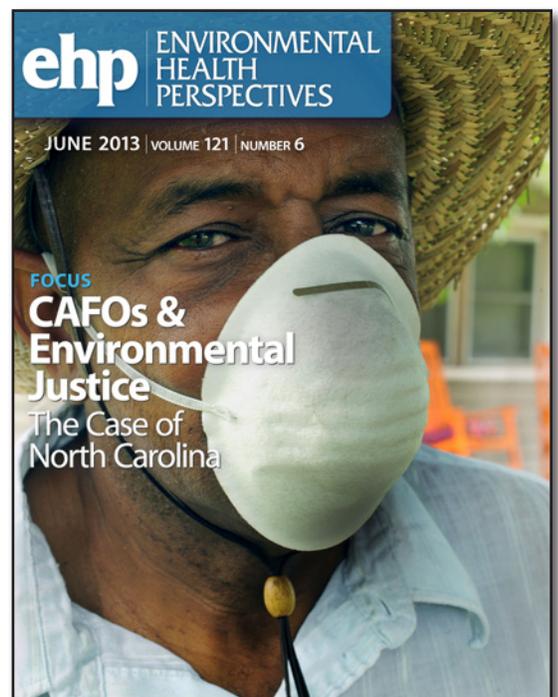
This month’s [Environmental Health Perspectives \(EHP\)](#) highlights environmental justice issues related to hog farming in North Carolina, and the matrix of risk for elevated blood lead in refugee children.

CAFOs and Environmental Justice: The Case of North Carolina

Although the Midwest is the traditional home for hog farms, with Iowa still the top-producing state, North Carolina went from fifteenth to second in hog production between the mid-1980s and mid-1990s. This growth — and the health impacts that accompany it — has clustered largely in the eastern half of the state, where concentrated animal feeding operations (CAFOs) are typically sited in low-income, black communities. As growing evidence demonstrates the adverse health effects of CAFO emissions, a handful of pioneers are experimenting with environmentally superior technologies in an effort to turn hog farms into better neighbors.



<http://twitter.com/ehponline>



Unsafe Harbor? Elevated Blood Lead Levels in Refugee Children

Refugee children from developing countries make up a segment of U.S. children at particular risk for elevated blood lead. Some children arrive in this country with elevated blood lead levels attributable to leaded gasoline, lead-glazed pottery, traditional medicines and folk remedies, and many other culture-specific routes of exposure. Others encounter lead hazards only after they immigrate, often a result of living in inexpensive housing with flaking lead-based paint. In educating refugees about lead hazards, public health workers must be sensitive to cultural ways and mindful of communication barriers.

Featured research and related news articles this month include:

- **Concentrations and Potential Health Risks of Metals in Lip Products** — Metals in Lip Products: A Cause for Concern?
- **Effects of Icelandic Eyjafjallajökull Volcanic Ash on Innate Immune System Responses and Bacterial Growth *in Vitro*** — Volcanic Ash and the Respiratory Immune System: Possible Mechanisms Behind Reported Infections
- **Residential Proximity to Methyl Bromide Use and Birth Outcomes in an Agricultural Population in California** — Getting the Drift: Methyl Bromide Application and Adverse Birth Outcomes in an Agricultural Area
- **Exercise Attenuates PCB-induced Changes in the Mouse Gut Microbiome** — Running Interference? Exercise and PCB-induced Changes in the Gut Microbiome

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Extramural papers of the month

By Nancy Lamontagne

- [Elevated numbers of copy number variants linked with autism](#)
- [How dietary omega-3s reduce tumor growth](#)
- [Air pollution associated with increased risk for serious birth defects](#)
- [Text mining improves chemical-gene-disease curation](#)

Read the current Superfund Research Program [Research Brief](#). New issues are published on the first Wednesday of each month.

Elevated numbers of copy number variants linked with autism

New results from the NIEHS-funded Childhood Autism Risks from Genetics and Environment (CHARGE) study show that children with autism had significantly more DNA deletions or duplications, known as copy number variants (CNV), than those with typical development. The researchers propose that a greater number of CNVs, especially those caused by duplication, could predispose people to autism.

The researchers examined data from 516 children with autism or typical development from the CHARGE study. The frequency of CNVs was significantly higher in the children with autism than for children with normal development. This remained true even after removal of rare and likely pathogenic events, showing that the CNVs consisted of more common variants not exclusively found in children with autism. The level of personal and social skills negatively correlated (Spearman's $r = -0.13$, $P = 0.034$) with duplication CNV load for the affected children. Communication ($P = 0.048$) and socialization ($P = 0.022$) scores showed the strongest associations.

The researchers say that finding an overall increase in genetic change in children with autism heightens the need to understand the basis of this variation. Although scientists know that environmental factors can affect the stability of the genome, the researchers note that it is not known if the increased CNVs found in the children with autism result from environmental exposures, nutrition, medical factors, lifestyle, genetic susceptibility, or combinations of many elements together.

Citation: Girirajan S, Johnson RL, Tassone F, Balciuniene J, Katiyar N, Fox K, Baker C, Srikanth A, Yeoh KH, Khoo SJ, Nauth TB, Hansen R, Ritchie M, Hertz-Picciotto I, Eichler EE, Pessah IN, Selleck SB. 2013. Global increases in both common and rare copy number load associated with autism. *Hum Mol Genet*; doi:10.1093/hmg/ddt136 [Online 27 March 2013].

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How dietary omega-3s reduce tumor growth

NIEHS grantees report a key mechanism by which dietary omega-3 fatty acids could reduce tumor growth and spread of cancer. The studies suggest that combining dietary omega-3 with some anti-cancer drugs could effectively treat cancers, while reducing potential side effects.

Cell and mouse experiments showed that epoxy docosapentaenoic acids (EDPs), which are metabolites of the omega-3 fatty acid docosahexaenoic acid, inhibit tumor growth and metastasis, by blocking the formation of new blood vessels. Administering a low-dose epoxide hydrolase inhibitor, along with EDPs, stabilized the EDPs in circulating blood, leading to approximately 70 percent inhibition of primary tumor growth and metastasis. The anti-cancer drugs sorafenib and regorafenib are FDA-approved kinase inhibitors that also inhibit epoxide hydrolase, and the researchers say that EDPs could provide a new way to block blood vessel growth, while reducing side effects in cancer patients.

The researchers also found that a metabolite of the arachidonic acid omega-6 fatty acid had the opposite effect of EDP, slightly increasing blood vessel growth and tumor progression in mice. This increase in blood vessel growth encourages wound healing and tissue repair.

Citation: Zhang G, Panigrahy D, Mahakian LM, Yang J, Liu JY, Stephen Lee KS, Wettersten HI, Ulu A, Hu X, Tam S, Hwang SH, Ingham ES, Kieran MW, Weiss RH, Ferrara KW, Hammock BD. 2013. Epoxy metabolites of docosahexaenoic acid (DHA) inhibit angiogenesis, tumor growth, and metastasis. *Proc Natl Acad Sci U S A* 110(16):6530-6535.

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Air pollution associated with increased risk for serious birth defects

Women in the San Joaquin Valley of California, who were exposed to the highest levels of carbon monoxide, nitrogen oxide, or nitrogen dioxide during their first eight weeks of pregnancy, were more likely to have a baby with spina bifida or anencephaly neural tube defects than women with the lowest exposure, according to an NIEHS-supported study. These results add evidence of a link between air pollution exposure and some birth defects.

The researchers used data from the California Center of the National Birth Defects Prevention Study, and the NIEHS-funded Children's Health and Air Pollution Study, to investigate whether air pollution in the San Joaquin Valley of California is associated with risks of five types of birth defects. After controlling for factors, such as maternal race/ethnicity, education, and multivitamin use, the researchers observed increased odds of spina bifida or anencephaly neural tube defects in the babies of women who experienced the highest levels of carbon monoxide, nitrogen oxide, or nitrogen dioxide exposure during their first eight weeks of pregnancy. Ozone exposure was associated with decreased odds of neural tube defects.

The adjusted odds ratio was 1.9 (95 percent confidence interval: 1.1, 3.2) for neural tube defects among those with the highest quartile of carbon monoxide exposure compared with those with the lowest exposure. Nitrogen oxide exposure showed similar effects with the highest quartile of nitrogen oxide exposure associated with neural tube defects (adjusted odds ratio = 1.8, 95 percent confidence interval: 1.1, 2.8), and the adjusted odds ratio for the highest quartile of nitrogen dioxide exposure was 1.7 (95 percent confidence interval: 1.1, 2.7).

Citation: Padula AM, Tager IB, Carmichael SL, Hammond SK, Lurmann F, Shaw GM. 2013. The association of ambient air pollution and traffic exposures with selected congenital anomalies in the San Joaquin Valley of California. *Am J Epidemiol* 177(10):1074-1085.

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Text mining improves chemical-gene-disease curation

NIEHS grantees report that text mining can help rank more relevant scientific research for inclusion in the [Comparative Toxicogenomics Database \(CTD\)](#). The CTD is a public resource that provides information on chemical-gene, chemical-disease, and gene-disease interactions that are manually curated from scientific articles.

The researchers used a text-mining approach that assigns each article a document relevancy score, with a high score indicating that the article is more likely relevant for the CTD. They tested this approach on 14,904 articles, covering seven heavy metals, and found that integrating text mining with their current system of manual curation helped prioritize more relevant articles, increasing productivity by 27 percent and novel data content by 100 percent.

Citation: Davis AP, Wiegers TC, Johnson RJ, Lay JM, Lennon-Hopkins K, Saraceni-Richards C, Sciaky D, Murphy CG, Mattingly CJ. 2013. Text mining effectively scores and ranks the literature for improving chemical-gene-disease curation at the Comparative Toxicogenomics Database. *PLoSOne* 8(4):e58201.

(Nancy Lamontagne is a science writer with MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

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Intramural papers of the month

By Heather Franco, John House, Mallikarjuna Metukuri, and Bailey Schug

- [DNA methylation could predict breast cancer risk](#)
- [The mechanism of action of a natural estrogenic compound](#)
- [Human mitochondrial DNA polymerase ineffectively repairs acrolein-induced adducts](#)
- [Coordinating DNA double strand break repair at both ends](#)

DNA methylation could predict breast cancer risk

NIEHS scientists have discovered DNA methylation in blood could prove to be an effective indicator of who will develop breast cancer. Using the NIEHS Sister Study, a nationwide cohort of women, ages 35-74, whose sister had breast cancer, researchers used DNA extracted from white blood cell samples and assessed methylation at 27,000 sites across the genome. The team also examined known risk factors for breast cancer and genotyped women for nine common polymorphisms associated with breast cancer risk.

Epigenetic modifications, including DNA methylation, are increasingly recognized as important determinants of gene transcription. The team found evidence that women who subsequently develop breast cancer have different blood methylation profiles than women who remain cancer free, and that these methylation differences are detectable months to years before the clinical diagnosis of breast cancer.

The scientists also found that epigenetic modifications were significantly more accurate in predicting who will develop breast cancer than the known risk factors and polymorphisms, although they caution their test is not yet accurate enough for clinical use. These findings hold promise for breast cancer detection and risk prediction through methylation profiling of blood. **(BS)**

Citation: [Xu Z](#), [Bolick SC](#), [DeRoo LA](#), [Weinberg CR](#), [Sandler DP](#), [Taylor JA](#). 2013. Epigenome-wide association study of breast cancer using prospectively collected Sister Study samples. *J Natl Cancer Inst* 105(10):694-700.

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The mechanism of action of a natural estrogenic compound

Researchers at NIEHS recently identified the mechanism of action for the natural estrogenic compound diarylheptanoid (D3). The work could have therapeutic implications for estrogen withdrawal symptoms in women.

D3s are abundant in spices and vegetables that possess estrogenic activity. In the present study, scientists used D3 isolated from the medicinal plant *Curcuma comosa*. They found that D3 activated an estrogen responsive element luciferase reporter through estrogen receptor alpha (ERalpha) in human cells, and mouse lacking ERalpha models. Their molecular modeling studies suggested that D3 could be accommodated in the ERalpha binding pocket. D3 also increased early-phase and late-phase estrogen-regulated gene responses in ovariectomized wild-type animals similar to 17beta-estradiol (E2). When administered together, D3 and E2 exhibited no additive or antagonistic effects.

The authors concluded that D3 acted as a weak agonist of ERalpha, without interfering with the effect of endogenous estrogens in the *in vivo* model. The finding may support the therapeutic use of this plant in ovarian cycling women. The authors also proposed that their three-dimensional molecular modeling studies may shed light on how other nonsteroidal endocrine-disrupting compounds exert estrogenic activity through ERalpha. **(MM)**

Citation: [Winuthayanon W, Piyachaturawat P, Suksamrarn A, Burns KA, Arao Y, Hewitt SC, Pedersen LC, Korach KS](#). 2013. The natural estrogenic compound diarylheptanoid (D3): *in vitro* mechanisms of action and *in vivo* uterine responses via estrogen receptor alpha. *Environ Health Perspect* 121(4):433-439.

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Human mitochondrial DNA polymerase ineffectively repairs acrolein-induced adducts

Researchers from NIEHS, in collaboration with scientists from Oregon Health and Science University, report that acrolein-induced adducts to mitochondrial DNA are bypassed by human mitochondrial DNA polymerase gamma at low fidelity, causing errors in DNA synthesis. Since these errors have the possibility of becoming mutations that could then lead to human diseases, such as neurodegenerative disorders, the research has implications for public health.

Acrolein is a mutagenic aldehyde produced by biological processes and by combustion of organic materials, including tobacco smoke. Acrolein reacts with bases on DNA to form adducts that block DNA synthesis. In the nucleus, DNA adducts are repaired by multiple translesion synthesis polymerases that don't exist in animal cell mitochondria.

The researchers utilized single nucleotide incorporation and primer extension analyses to assess if mitochondrial polymerase gamma was able to overcome acrolein-induced DNA adducts in mitochondrial DNA. They found adenosine adducts were correctly and efficiently repaired. However, repair of minor groove guanine adducts, although able to be bypassed by pol gamma, exhibited reduced efficiency and low fidelity with a preference for incorporation of opposite-adduct purines. **(JH)**

Citation: [Kasiviswanathan R, Minko IG, Lloyd RS, Copeland WC](#). 2013. Translesion synthesis past acrolein-derived DNA adducts by human mitochondrial DNA polymerase gamma. *J Biol Chem*; doi:10.1074/jbc.M113.458802 [Online 30 March 2013].

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Coordinating DNA double strand break repair at both ends

Utilizing a novel technology they developed, researchers in the NIEHS Chromosome Stability Group were, for the first time, able to directly observe an essential event in an evolutionarily conserved process of repair of DNA double-strand breaks (DSBs). They also established a key role for a clinically relevant protein complex in this initial step of DNA repair, providing insight into human health conditions.

Through 2-D pulsed-field gel electrophoretic mobility shift assay analysis of mutant yeast strains, lead researcher James Westmoreland demonstrated coincident resection at both ends of DSBs and showed that the process is coordinated by the MRX complex and Sae2 proteins. Unexpectedly, he found that the necessity of these proteins in coincident resection differed depending on the type of DSB with a stronger requirement at dirty breaks, which are more similar to those that occur naturally as a result of various environmental agents.

Not only does this study establish a new technique that can be adapted in future studies to other organisms, but it also demonstrates the importance of a specific protein complex in the repair of DNA breaks. Further, as the genes that encode these proteins are mutated in multiple diseases, these results have important implications for human health. **(HF)**

Citation: [Westmoreland JW, Resnick MA](#). 2013. Coincident resection at both ends of random, gamma-induced double-strand breaks requires MRX (MRN), Sae2 (Ctp1), and Mre11-nuclease. PLoS Genet 9(3):e1003420.

(Heather Franco, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Laboratory of Reproductive and Developmental Toxicology. John House, Ph.D., is an IRTA fellow in the NIEHS Laboratory of Respiratory Biology. Mallikarjuna Metukuri, Ph.D., is a research fellow in the NIEHS Laboratory of Signal Transduction. Bailey Schug studies health promotion and nutrition at Appalachian State University and is an intern in the NIEHS Office of Communications and Public Liaison.)

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Inside the Institute

NIEHS employees flex muscles during Health and Fitness Week

By Eddy Ball

As they do each year, NIEHS employees and contractors turned out to celebrate the Institute's rites of spring — the full schedule of competitions and activities that make up Health and Fitness Week. This year's Seattle-like spring weather April 29-May 3 meant the cancellation of the Obstacle Course, but the drizzles and threats of rain failed to detour enthusiasts from indoor events or from the high-profile muscular outdoor competitions.

Highlighting the week were the annual 2-mile nature walk and Rogathon 5K run, which consistently draw the biggest crowds of the week. The Rogathon is named for a longtime champion of the fun run, NIEHS epidemiologist Walter Rogan, M.D.

Health and Fitness Week is always an affair where the process is more important than the outcome. The laurels rarely fall very far from the group of serial winners, but that doesn't seem to discourage anyone from fully enjoying the games and good-natured competition. Whether they place first or last, most participants are justifiably proud of being a part of the annual celebration.

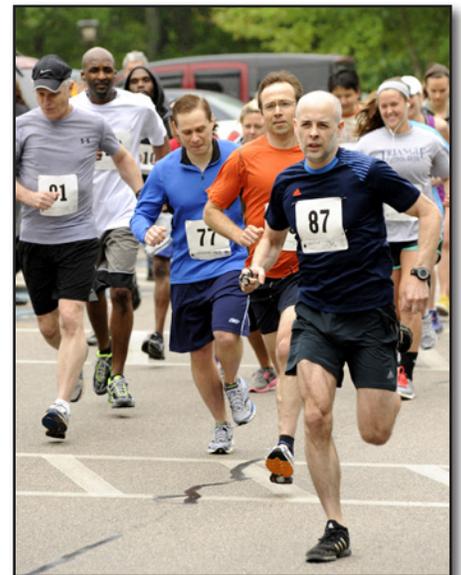
Health and Fitness Week takes place during National Physical Fitness and Sports Month, which is designated each year by Presidential proclamation. The fun-filled week is organized and coordinated by members of the NIEHS Office of Management (OM) Health and Safety Branch (HSB) and Administrative Services and Analysis Branch.



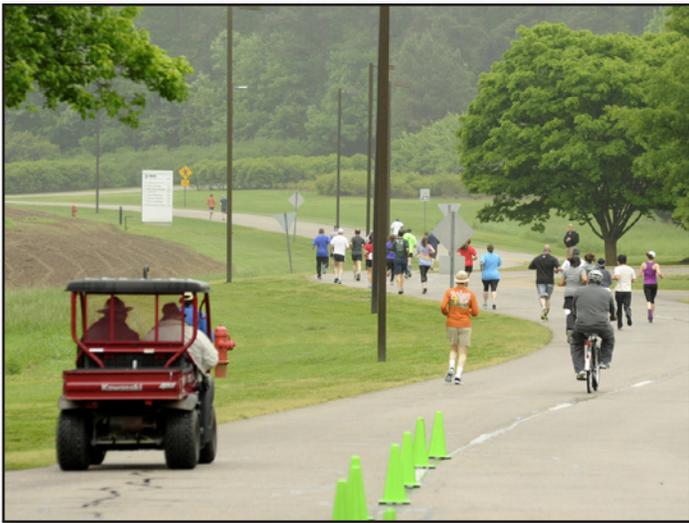
An exuberant April Lane, center, of OM, led the participants in the nature walk, as they started at the NIEHS main building. Several trekkers, such as Jennie Foushee, left, of the Division of Intramural Research (DIR), brought along umbrellas, in case the drizzle became heavier during the walk. (Photo courtesy of Steve McCaw)



Employee Services Manager Ed Kang flashed the victory sign confidently, as he and smiling colleagues from OM made their way along the route. (Photo courtesy of Steve McCaw)



As the Rogathon began, most of the runners were trying too hard to get a good start, to spend much time in smiling and banter. Leading the pack were DIR scientists Tim Gingerich, Ph.D., front, a visiting fellow, and lead researcher Lars Pedersen, Ph.D., next to him in orange, who ended up sharing first place in the competition. (Photo courtesy of Steve McCaw)



HSB safety officer Chris Hunt and colleagues followed behind the runners, to make sure the route through the misty campus was clear of traffic and the athletes remained healthy during the run. (Photo courtesy of Steve McCaw)



Unlike the runners who passed them by, nature walk participants had some opportunity to socialize along the route. Dudley Riner, left, of OM, chats with DIR visiting fellows Natacha Steinckwich-Besancon, Ph.D., and Felicity Davis, Ph.D., right. (Photo courtesy of Steve McCaw)



As she has for several years, HSB industrial hygienist VeeVee Shropshire was on hand, and dressed for the occasion, to help coordinate activities. (Photo courtesy of Steve McCaw)



With the initial pressure of the starting line behind them, some of the participants, including Kristen Fisher of OM, took advantage of opportunities to clown for the camera. (Photo courtesy of Steve McCaw)



Back from a two-year break from competition, lab chief Bill Copeland, Ph.D., was serious about his performance. His dedication paid off, as Copeland placed first in his age group. (Photo courtesy of Steve McCaw)



Health and Fitness Week basketball competition is good natured, but as the determination evident in the expression of NIEHS fellow Andrew Oldfield, Ph.D., suggests, it's still a competition that requires players to give their all. (Photo courtesy of Steve McCaw)

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Eric Potts, right, took to the air as Randy Hardy tried in vain to block the shot. Potts, Gordon Caviness, and Sha-mel Riggins won first place, overcoming the best efforts of the second-place team, Hardy, Oldfield, and Mark Rubino, and third-place winners William Boyd, Ken Coffey, Caranza Smith, and Ron Altiery. (Photo courtesy of Steve McCaw)

Mueller talks weird science at RTP event

By Eddy Ball

NIEHS staff scientist Geoffrey Mueller, Ph.D., was one of ten local scientists featured April 16 in the [Research Triangle Foundation 180 Degree series](#) event Weird Science. The series of events is designed to celebrate the collaboration between the Research Triangle, N.C., universities, companies, and communities. [Mueller](#), a structural biologist, discussed “The Structural Characterization of Allergens.”



Mueller is part of the NIEHS Nuclear Magnetic Resonance Group headed by Robert London, Ph.D. He said his interest lies in decoding allergic reactions. “What is it about those few specific proteins that become allergens that makes them special?” (Photo courtesy of Steve McCaw)

Linked video:
[Watch Mueller's talk at the Research Triangle Foundation event \(04:38\)](#)

(Launches in new window)

Download Media Player: Flash [🔗](#)

Emceed by entrepreneur and comic Will Hardison, the event was an entertaining combination of stand-up comedy and unusual science, delivered rapid-fire in audience-friendly five-minute segments. Topics ranged from the mind-boggling potential of the new [Geomagic](#) 3D printing technology, which makes off-the-grid design and manufacture of products, tools, and even weapons possible, to the utterly gross sample collection practices of Duke University biologist [William Parker, Ph.D.](#), who catches his own rats to study their intestinal parasites as part of his research into gut biology.

The fast-paced presentation by Mueller fell somewhere in the middle range on the scale of weirdness. His magnified images of a dust mite and the guts of eviscerated cockroaches could be described as gross, but Mueller was entirely serious when it came to his commitment to understanding inappropriate immune responses that threaten human health and sometimes even human life.

After all, Mueller told the audience, “I work at the National Institute of Environmental Health Sciences, and we like to think of what we do as very serious science.” By determining crystallographic structures of proteins, Mueller and other structural biologists are gaining new insights into the mechanisms involved in allergic reactions, and discovering new potential targets for developing safer forms of immunotherapy to reverse the allergic process.

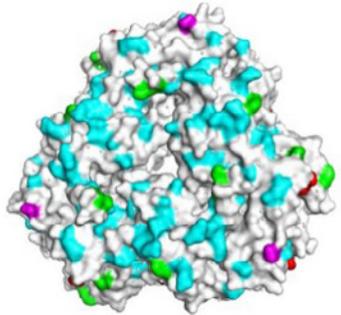


Structural Characterization of Allergens

180° - Weird Science
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Mueller focused on the most common allergies to indoor and outdoor exposures and food among people in North America — cockroach dander, periwinkle pollen, peanuts, and dust mite dander. (Image courtesy of Geoffrey Mueller)

Human Health Applications: 1 How do you become sensitized?



Ara h 1 (Peanut Allergen)
Chruszcz M, Maleki SJ, et al. 2011

Red and Magenta are sites of modification thought to influence immune system recognition.

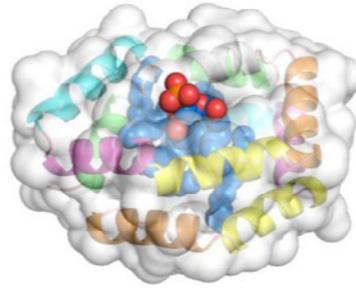
Crystallographic imaging allows scientists to see what otherwise would remain hidden. Mueller’s team mapped onto Ara h 1 peanut protein sites that are modified during the cooking process. (Image courtesy of Geoffrey Mueller)

Entomology: Cockroach Digestion

Eviscerated Cockroach
Normal Minus Bla g 1



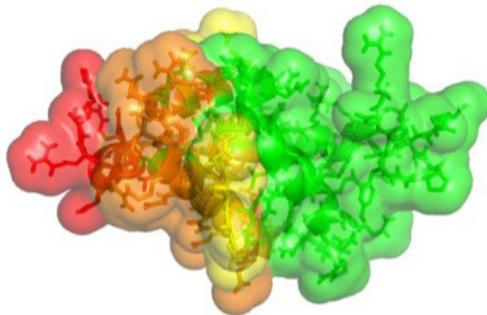
Suazo, Gore, & Schal (2009)



Bla g 1

The German cockroach gene Bla g 1 appears to regulate fat formation, shown in blue. Unfortunately for people looking for a weight control miracle, Mueller said humans don't have a counterpart to that gene, although they are allergic to the protein that Bla g 1 encodes. (Image courtesy of Geoffrey Mueller)

Human Health Applications: 2 How do you become DE-sensitized?



Peanut Allergen: Ara h 2

50% of patient uniquely recognize the red region of the molecule.

Design a safer allergy shot by modifying this region of the allergen.

According to Mueller, this discovery marks the point where basic science findings have the potential for translation into strategies to improve human health. (Image courtesy of Geoffrey Mueller)

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